THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MAY, 1947

ORIGINAL ARTICLES

STUDIES IN THE ORAL ADMINISTRATION OF PENICILLIN

I. ASSAYS OF VARIOUS PREPARATIONS AND THE DETERMINATION OF THE EFFECTIVE THERAPEUTIC DOSE*

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ASSAY OF ORAL PENICILLIN. It is now well established that the oral administration of penicillin can produce therapeutic plasma penicillin levels in spite of the fact that a portion of the penicillin is destroyed when in contact with gastric acid. Even before the Committee on Chemotherapeutic and Other Agents of the National Research Council had sanctioned the oral use of penicillin,[7,11] a number of clinical reports of the therapeutic value of this dosage form had appeared.[3,4,10] Gonorrhea and pneumococcic pneumonia have been shown to respond as readily to penicillin given orally as to that parenterally injected, and isolated examples of infection by other organisms sensitive to penicillin have been reported successfully treated by this procedure.

However, there are some poorly understood features of the problem of penicillin medication by mouth. The general practitioner has been given the impression either by direct statement or by implication that oral penicillin is worth while chiefly as an adjuvant for parenteral penicillin after the temperature has subsided or for mild cases of infection and that it should not be used for any severe infection. He has also been led to believe that if penicillin by mouth is used under such circumscribed conditions the determination of the most effective dosage is not too important and that there need not be any concern over plasma penicillin levels or over the relation of the latter to penicillin sensitivity of the bacterium involved.

One important basis for this confused therapeutic reasoning has been that penicillin is inordinately expensive and that the quantities available for general distribution are limited and likely to remain so. Thus, although penicillin is no more harmful in large doses than in smaller ones, the therapeutic approach has been paradoxically to determine not the optimal but the minimal effective dose. Obviously, if price or limitations of supply were not involved, such an attitude would be recognized as therapeutically unsound. The consequences of such a point of view have been to tend to discredit oral penicillin and to reduce it almost to the category of a tonic.

* Aided by a grant from the Commercial Solvents Corporation, Terre Haute, Indiana.

The present investigation, begun before oral penicillin was made generally available, was undertaken with the purpose of determining, if possible, the ultimate potentialities and the limitations of this therapeutic method. The hope was to achieve in oral penicillin a dosage form as adequate and as effective as that of parenterally injected penicillin, without the annoyance and pain and technical limitations of the latter. The present report deals with the assay of a number of oral preparations in order to determine an effective dosage. In the succeeding papers reports are made of the therapeutic results based on this dosage.

Method. Estimations of plasma penicillin concentration were made by *B. subtilis* serial dilution method of Randall, Price and Welch[6] as modified by Hickey.[5] In this modification, the multiple pipettings were made with a sterile pipetting machine and the inoculum used was a nutrient broth dilution (1.5 cc. to 100 cc.) of an 18 hour nutrient broth culture of *B. subtilis* (NNRL-B–558). The latter were prepared daily from stock agar slants by incubation on a shaking machine at 30° C. Serial dilutions of a standard penicillin solution (1 unit per cc. in a phosphate buffer at pH 6) usually produced 6 tubes with no growth. Thus an unknown serum similarly diluted and also producing 6 clear tubes would contain 1 unit per cc. The lower limit of penicillin concentration that could be estimated with such a standard was 0.031 unit per cc. Occasionally the standard showed 7 clear tubes which allowed measurements to 0.016 unit per cc. To insure greater accuracy of measurement 3 standard series were prepared for each day of assays. The results were discarded if the standards did not give consistent measurements. Blood was drawn for penicillin levels under aseptic conditions and transferred to tubes containing 0.02 gm. sodium citrate. The plasma was separated and used for the analyses. Serum was found to give the same values but its separation under sterile conditions proved inconvenient.

It has been alleged that *B. subtilis* has doubtful value as an organism for estimation of plasma penicillin level because many blood specimens contain inhibitors of this bacterium even when penicillin is not present.[1,2] To test this statement, control blood samples were taken for penicillin estimation before penicillin was administered in 40 assays. In addition, blood specimens from 80 hospital patients not on penicillin or sulfonamide therapy were analyzed for penicillin. In the total of 120 plasma specimens, only 1 showed a level equivalent to 0.03 unit; the rest gave zero levels. These findings, supplemented by the many zero levels in the hundreds of assays made during the studies, have convinced us that at least with our use of the method and possibly because of the employment of citrated plasma, there is little danger of finding positive penicillin levels in plasma specimens that do not contain penicillin.

The subjects used for assay of the various oral preparations of penicillin were so-called hospital controls, that is, those patients who were not acutely ill and who were believed not to have any circulatory or renal disturbances. They were, for the most part, young or middle-aged persons recuperating from herniorrhaphy or convalescing from some acute illness such as fracture, burn, or traumatic wound. After preliminary experiments had confirmed the now well-established fact that plasma penicillin levels were lower when penicillin was given after a meal than on an empty stomach, the routine established for assays was to give single doses of penicillin at 9 A.M., some 2 hours after breakfast. Blood samples were drawn at varying intervals after the dose without regard to the noon meal. When a priming dose was to be given first, this was administered at 8 A.M., and the second dose at 9 A.M., the time being counted from the second dose.

The oral preparations utilized in these studies were with 1 exception, especially prepared for us. Control studies were made with capsules containing crude calcium penicillin of about 700 units per mg. potency. These were put up in hard gelatin capsules and contained no buffer or

other diluent. These were called Capsules C. They were of several sizes: 25,000, 33,000 and 100,000 units per capsule. Capsules R.B. contained 25,000 units of the same crude calcium penicillin buffered with pectin hydrolysate. Capsules No. 10 contained 100,000 units of crystalline potassium penicillin, each containing 100,000 units. A variety of tablets were studied, most of which contained as the chief protecting agent a high melting fat. Some of these were discarded after only a few experiments. The tablets containing citrate were a marketed preparation. A brief description of those capsules and tablets on which extensive assays have been made is given in Table 1.

TABLE 1.—DESCRIPTION OF PENICILLIN CAPSULES AND TABLETS INVESTIGATED

Name	Type of penicillin	Diluent or buffer	Units per capsule or tablet
Capsules C	Crude calcium, 700 units per mg.	None	25,000; 33,000; 100,000
Capsules R. B.	Crude calcium, 700 units per mg.	Pectin hydrolysate	25,000
Capsules No. 10	Crystalline potassium, 1510 units per mg.	None	100,000
Capsules No. 11	Crystalline ammonium, 1500 units per mg.	None	100,000
Capsules No. 23	Crystalline potassium	Basic alum. acetate	25,000
Tablets No. 18	Crystalline potassium	Hydrogenated fat; soaps; starch	50,000; 100,000
Tablets No. 24	Crystalline potassium	Hydrogenated fat; soaps; mg. stearate	100,000
Tablets No. 35	Crystalline potassium	Sodium benzoate	50,000
Tablets No. 38	Crystalline potassium	Sodium sulfanilate	50,000

ASSAYS OF VARIOUS ORAL PREPARATIONS. *Criteria for Effective Plasma Penicillin Levels.* There has been no agreement as to what plasma penicillin concentration should be achieved to assure therapeutic effectiveness. The difficulty in estimating this concentration arises on the one hand from the variability in sensitivity to penicillin of the different organisms and the various strains of the same organism, and on the other hand from the rapidly changing plasma penicillin levels produced by the administration of penicillin. Findland and his colleagues[5] have shown that most organisms sensitive to penicillin, especially gonococci and pneumococci, are inhibited in concentrations of less than 0.03 unit per cc. However, they, as well as all other investigators in this field, are aware of the fact that many so-called sensitive organisms are not inhibited except by much higher concentrations than 0.03 unit per cc. Under any circumstance it is dangerous to translate directly such *in vitro* findings to *in vivo* conditions. Plasma penicillin levels should certainly be at least as high as that required for *in vitro* inhibition. They should probably be much higher if only to give assurance that all body fluids likely to contain the invading organism continuously have an effective penicillin concentration. Such an idea receives confirmation from the now well-established empirical finding that doses of 20,000 units of penicillin intramuscularly every 3 hours are effective in most acute infections responsive to penicillin. Such injections have been found by us[6] to give plasma levels, as determined by the *B. subtilis* method of assay, of 0.5 unit per cc. at ½ hour, 0.06 at 2½ hours and 0.03 at 3 hours. It appears from these considerations that the desirable plasma penicillin levels should be at least 0.03 unit per cc. at any time and higher than 0.06 most of the time. These criteria have been used as a guide in the determination of the required dosage of oral penicillin.

Dosage of 25,000 Units. Plasma penicillin levels determined after single or even repeated doses of 25,000 units proved dis-

appointing. Rarely were levels encountered higher than 0.03 unit per cc. Most frequently no perceptible levels were obtained. There were so many zero levels and there was so little difference between the various preparations, that it was useless to tabulate the results.

the least being obtained with the tablets buffered with sodium citrate. The levels in the third interval tended to be higher, but for the most part they ranged between 0.03 and 0.06 unit per cc., with an occasional 0.125 and a rare 0.25 unit per cc. The citrated tablets gave a higher average.

TABLE 2.—FREQUENCY DISTRIBUTION OF PLASMA PENICILLIN LEVELS AFTER FIRST AND THIRD DOSE OF 50,000 UNITS OF PENICILLIN GIVEN ORALLY EVERY 2 HOURS FOR 3 DOSES

Type of medication	Interval	Hour	Plasma penicillin concentration (units per cc.) 0(<0.03)	0.031	0.062	0.125	0.25	Arithmetica mean
Capsules C	First	½	10	3	1	..	..	0.011
		2	9	3	2	..	..	0.015
	Third	½	6	4	3	1	..	0.028
		2	6	7	1	..	..	0.019
Capsules R.B.	First	½	9	3	1	..	..	0.012
		2	8	5	..	..	..	0.012
	Third	½	4	8	1	..	..	0.024
		2	6	6	1	..	..	0.019
Capsules No. 23	First	½	5	4	3	..	..	0.025
		2	7	3	2	..	..	0.016
	Third	½	2	6	3	1	..	0.038
		2	3	6	3	..	..	0.030
Crystalline potassium penicillin in water	First	½	8	2	2	..	..	0.015
		2	5	6	1	..	..	0.020
	Third	½	..	5	5	2	..	0.053
		2	2	8	1	1	..	0.033
Tablets No. 18	First	½	7	6	1	..	..	0.017
		2	5	6	3	..	..	0.026
	Third	½	2	7	4	1	..	0.039
		2	1	7	4	2	..	0.047
Tablets No. 35	First	½	3	7	1	1	..	0.030
		2	6	4	..	2	..	0.025
	Third	½	1	6	4	..	..	0.045
		2	1	6	4	1	..	0.043
Tablets No. 38	First	½	9	3	5	2	1	0.045
		2	9	8	3	..	..	0.022
	Third	½	3	6	9	2	..	0.050
		2	7	8	3	2	..	0.034
Tablet with sodium citrate (commercial)	First	½	2	6	3	1	..	0.038
		2	1	2	7	2	..	0.055
	Third	½	1	2	6	3	..	0.058
		2	1	3	6	2	..	0.053

Dosage of 50,000 Units. On the possibility that 50,000 units of penicillin every 2 hours might be a satisfactory oral dosage of penicillin, 8 different preparations were assayed as follows: 50,000 units were given to hospital control subjects every 2 hours for 3 doses, and blood was drawn at ½ and 2 hours after the first and after the third dose. A total of 109 assays involving 436 plasma penicillin level determinations were carried out. The results are summarized in Table 2. There were a large number of zero levels, particularly in the first interval for all the preparations, chiefly because they produced fewer zero levels. In general the data indicated that while it was possible to attain therapeutic penicillin levels with doses of 50,000 units given every 2 hours, there were still too many zero levels and too few 0.125 or higher levels to make this dosage as reliable for use in severe infections as that of 20,000 units parenterally every 3 hours. The data also indicated that, with the exception of the lowered tendency to zero levels shown by the citrated preparations, there was no great difference in the various preparations.

That the prevailing plasma levels were higher in the third interval than in the first was undoubtedly due to the "priming" effect of the first 2 doses. Penicillin with the first doses was distributed to all the body fluids leaving a residual concentration at the end of each interval which, though not necessarily high enough to be measurable, allowed the attainment of a higher level with the succeeding doses. In the parenteral administration of penicillin there is little use for this priming effect, for the plasma levels immediately after the injection are so high as to be little affected by residual penicillin concentrations from the previous dose. But with orally administered penicillin where the absorption is slow and where the early plasma concentrations are not so great as those obtained with parenteral injections, the priming effect of the previous doses becomes an important factor in helping achieve therapeutic concentrations, as in the oral administration of sulfa compounds. This finding was made use of in the establishment of the therapeutic regimens.

Dosage of 100,000 Units. Preliminary experiments with oral doses of 100,000 units of penicillin demonstrated that a satisfactory range of plasma levels could be achieved. For the purpose of simulating in single assays the conditions obtaining when doses of 100,000 units were used in actual therapy after a larger priming dose of 200,000 units, a series of comparative assays of the various oral preparations was made in which 200,000 units were administered at 8 A.M., followed by 100,000 units at 9 A.M., blood being drawn at intervals after the 9 A.M. dose. The plasma levels obtained were found to be of the same order as those in the therapeutic studies to be reported.

Table 3 shows the frequency distribution of plasma penicillin levels with one of the preparations studied, crystalline potassium penicillin in gelatin capsules (Capsules No. 10). The levels were determined for ½ hour periods after the 9 A.M. dose of 100,000 units, but in any single assay no more than 4 determinations were carried out. However, by the use of a large number of assays with penicillin determinations made at varying intervals, it was possible to cover each ½ hour period up to 5½ hours. From Table 3 it can be seen that there was a marked variability in the plasma levels at any period, much greater than that found after parenteral injections of penicillin. Several types of averages were determined for each period: mode, median, arithmetical mean and "weighted average." The last, a form of the geometric mean, was obtained by giving a linear weighting—1 for values less than 0.03, 2 for 0.03, etc.—for each of the geometrically progressing plasma penicillin levels, determining the arithmetical mean of these values, and transposing back into units per cc. The conclusions that can be drawn from the data are the same whichever form of average is utilized, but since the weighted average appears to give the smoothest curves, it has been used in the comparisons of the various preparations.

During the 1st hour, the range of pen-

TABLE 3.—DISTRIBUTION OF PLASMA PENICILLIN LEVELS AFTER ADMINISTRATION OF PENICILLIN CAPSULES NO. 10 IN A DOSE OF 200,000 UNITS FOLLOWED IN 1 HOUR BY 100,000 UNITS IN 52 SUBJECTS

Weighted value	Units (per cc.)	Hours after administration of 100,000 units										
		½	1	1½	2	2½	3	3½	4	4½	5	5½
6	0.5	1	3	..	..	..	1					
5	0.25	4	4	4	4	..	4					
4	0.125	7	6	4	2	3	4	..	2	3		
3	0.062	..	1	3	3	4	3	3	4	2	2	1
2	0.03	2	2	1	4	4	8	6	2	4	5	
1	0	..	..	..	..	1	3	3	9	8	12	12
Average	..	0.174	0.211	0.143	0.120	0.063	0.106	0.031	0.034	0.037	0.020	0.005
Mode	..	0.125	0.125	0.125	?	0.06	0.03	0.03	0.0	0.0	0.03	0
Median	..	0.125	0.125	0.125	0.06	0.06	0.06	0.03	0.03	0.03		
Weighted average	..	0.138	0.163	0.122	0.087	0.056	0.057	0.04	0.03	0.03	0.018	0.012

icillin levels after the administration of capsules of potassium penicillin was from 0.5 to 0.03 unit per cc. The modal and median values were 0.125 unit per cc. and the arithmetical and geometrical mean were both between 0.125 and 0.25 unit per cc. The peak mean value appeared in this series to be at 1 hour, but it might be that the difference between the values at 1 hour and those at ½ hour was not significant. There were no zero values during the first 2 hours. At 3 hours a considerable number of zero units per cc. concentrations began to appear, and at 4 hours it became the prevailing concentration. Yet, even at 5 hours, 7 out of 19 determinations were 0.03 unit per cc. or higher. The averages obtained over the 5 hour period indicate that though the initial levels were not usually as high as those obtained with single parenteral injections of 20,000 units, nevertheless good therapeutic levels were maintained for at least 3 and possibly for 4 hours.

A comparison of 8 different preparations in assays made after a priming dose of 200,000 units followed in 1 hour with a dose of 100,000 units as shown in Table 4. The weighted average as determined above was used as the basis for comparison. The most striking feature of these data was that there was on the whole very little difference in the levels achieved, no matter what preparation was used. Crude penicillin alone in capsules produced almost the same values as did crude penicillin protected with pectin. Pure potassium penicillin gave levels not greatly different from potassium penicillin protected with a high melting fat. However, several types of tablets, 1 of which, Tablet No. 24, is shown in Table 4, apparently disintegrated too slowly to give as high levels as the other preparations. A slight distinction between the various preparations seemed to be present at the 4½ and 5 hour period. At this stage only Capsules No. 10, Tablets No. 18 and probably penicillin tablets containing citrate appeared to produce any significant plasma penicillin levels, usually 0.03 unit per cc. On the whole, the data imply that almost any form of penicillin, if given in doses of 100,000 units after a priming dose, will produce good plasma levels persisting in the therapeutic range for 3 or more hours. If this dose were used every 3 hours, a residual plasma (and body fluid) concentration would tend progressively to raise the plasma level with each dose.

Table 4.—Comparison of Average Values for Plasma Penicillin Levels After Administration of 200,000 Units Followed in 1 Hour by 100,000 Units for Various Types of Capsules and Tablets

No. subjects	Preparation	Hours after administration of 100,000 units										
		½	1	1½	2	2½	3	3½	4	4½	5	5½
49	Tablets No. 18	0.150	0.163	0.119	0.119	0.059	0.062	0.044	0.034	0.034	0.025	0
52	Capsules No. 10	0.138	0.163	0.119	0.088	0.056	0.059	0.039	0.031	0.031	0.18	0.012
29	Capsules No. 11	0.213	0.106	0.110	0.073	0.056	0.046	0.046	0.031	0.016	0.006	0
19	Tablets No. 24	0.031	0.062	..	0.034	..	0.034	..	0.016	..	0.016	.
35	Capsules R.B.	0.275	0.125	0.150	0.125	..	0.100	..	0.039	0.016	0.012	0
35	Capsules A control	0.163	0.138	0.110	0.073	..	0.049	0.028	0.034	0.003	0.006	0
25	Tablets with sodium citrate (commercial)	..	0.210	..	0.119	..	..	..	0.043	..	..	0.007

A comparison of 8 different preparations in assays made after a priming dose of 200,000 units followed in 1 hour with a dose of 100,000 units as shown in Table 4. The weighted average as determined above was used as the basis for comparison. The most striking feature of these data was that there was on the whole very little difference in the levels achieved, no matter what preparation was used. Crude penicillin alone in capsules produced almost the same values as did crude penicillin protected with pectin. Pure potassium penicillin gave levels not greatly different from potassium penicillin protected with a high melting fat. However, several types of tablets, 1 of which, Tablet No. 24, is shown in Table 4, apparently disintegrated too slowly to give as high levels as the other preparations. A slight distinction between the various preparations seemed to be present at the 4½ and 5 hour period. At this stage only Capsules No. 10, Tablets No. 18 and probably penicillin tablets containing citrate appeared to produce any significant plasma penicillin levels, usually 0.03 unit per cc. On the whole, the data imply that almost any form of penicillin, if given in doses of 100,000 units after a priming dose, will produce good plasma levels persisting in the therapeutic range for 3 or more hours. If this dose were used every 3 hours, a residual plasma (and body fluid) concentration would tend progressively to raise the plasma level with each dose.

Larger Doses. In isolated experiments, single doses from 200,000 to 360,000 units of varying preparations have been used for assays, blood specimens being taken up to 6 hours after the dose. In most of these the levels achieved in the 1st hours were not greatly different from those for 100,000 with a 200,000 unit priming dose. However, there was a greater tendency for prolongation of penicillin levels to 6 hours. In another group of experiments, Tablets No. 18 were given in doses of 200,000 units every 8 hours for 3 doses and blood levels taken after the last dose. The results are shown in Table 5. It can be seen that the levels were not much higher in the 1st hour than those found after administration of a priming dose of 200,000 units

followed in 1 hour by 100,000 units. However, the significant finding was that appreciable levels were usually present at 6 hours after the last dose and not infrequently after 8 hours. These results would seem to indicate that there would be little harm in giving a double dosage before bedtime and allowing the patient to go through the night without being awakened for further penicillin medication.

Doses of 100,000 units, when preceded by a primary dose of 200,000 units 1 hour earlier, gave levels averaging higher than 0.125 unit per cc. for the first 2 hours and about 0.06 unit for the next 2 hours. Such levels were comparable with those achieved, but there were too many zero levels and too few levels higher than 0.06 unit per cc. to make the dosage a reliable substitute for parenteral therapy.

TABLE 5.—PLASMA PENICILLIN LEVELS AFTER ADMINISTRATION OF TABLETS NO. 18 IN DOSES OF 200,000 UNITS EVERY 8 HOURS FOR 3 DOSES

Subject	Hours after third dose (units per cc.)							
	1	2	3	4	5	6	7	8
Se.	..	0.25	..	0.125	..	0.125	..	0.06
Ba.	..	0.25	..	0.125	..	0.125	..	0
McI.	..	0.5	..	0.25	..	0.125	..	0.03
HI.	..	0.5	..	..	..	0.25	..	0.06
Hi.	..	0.25	..	0.06	..	0.06	..	0
Ro.	..	0.03	..	..	..	0.06	..	0.03
Jo.	0.06	..	0.06	..	..	0.125	..	0.06
Be	0.03	..	..	..	..	0.03	..	0.03
Re.	..	..	0.25	..	..	0.06	..	0
Fr.	..	0.125	..	..	..	0.03	..	0
Co.	..	0.25	..	..	..	0.06	..	0.03
Ka.	..	0.06	..	..	..	0.03	..	0

Doses of 25,000 units were ineffective usually in producing appreciable plasma penicillin levels. When 50,000 units were administered every 2 hours, plasma levels of 0.06 unit per cc. were frequently obtained with intramuscular injections of 20,000 units every 3 hours. At this dosage there were no great differences in the results with the various preparations.

Doses of 200,000 units gave perceptible plasma levels even at 6 and 8 hours after the dose.

From these findings, the therapeutic regimen established was a primary dose of 200,000 units followed by 100,000 units every 3 hours.

Summary and Conclusions. Assays of the plasma penicillin levels achievable with varying doses of penicillin orally administered were made with a large variety of preparations, with and without diluents, anti-acid substances, or buffers.

The authors wish to acknowledge their indebtedness to Mrs. Ellen Zimmermann, Mrs. Jeanne Hildebrandt and Miss Margaret Casella for their technical assistance.

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STUDIES IN THE ORAL ADMINISTRATION OF PENICILLIN

II. Results of Treatment of Pneumococcic Lobar Pneumonia and Other Acute Infections with Several Oral Penicillin Preparations*

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Oral Penicillin Therapy. In a series of assays of capsules and tablets of penicillin designed for oral use, it has been shown[2] that doses of 100,000 units every 3 hours, preceded by a primary dose of 200,000 units, would give therapeutically effective plasma penicillin levels, comparable with those obtained with 20,000 units intramuscularly every 3 hours. With this basis for therapy, a series of patients with bacterial infections known to be responsive to penicillin were treated by oral administration of several of the preparations assayed. This paper is a report of the results of such treatment.

The patients studied could be divided into 2 groups: those having pneumococcic lobar pneumonia and those having a miscellaneous group of infections other than pneumonia. In all cases an attempt was made to determine the causative organism, to obtain confirmation of the diagnosis by Roentgen ray if possible, to get white cell counts and temperature curves, and to determine representative plasma penicillin levels. However, in a large group of cases, no such control could be obtained. Since in these cases only a clinical evaluation could be used to measure the success of the treatment, they have not been included in the tabulation of results. They are, however, included in the evaluation of toxic reactions.

The regimen established was as follows: As soon as the clinical diagnosis was made, a dose of 200,000 units of penicillin was administered orally. Then, 100,000 units were given orally every 3 hours on a 3, 6, 9 and 12 o'clock schedule. This schedule avoided all meals, except the noon meal, since these were given at 7, 11:30, 4:30 and 8 o'clock (evening nourishment). No other effort was made to rule out the effect of food on the absorption of penicillin. The medication was continued for at least 3 days or usually at least 48 hours after the temperature had returned to normal. The usual sustaining medication was allowed, especially codein sulfate for cough; but aspirin was not permitted because of its possible antipyretic effect. Parenteral fluids and oxygen were administered if necessary.

Pneumococcic Lobar Pneumonia. Since the purpose of these therapeutic studies was to determine merely whether orally administered penicillin could accomplish everything that parenterally injected penicillin has been known to do, the patients chosen for the most part were manifest cases of uncomplicated pneumonia. However, since the decision for the initial treatment was in the hands of the interne (the majority of patients with pneumonia being admitted during the night) many doubtful cases were chosen. Where later clinical examination, laboratory finding and Roentgen ray evidence indicated a mistake in the diagnosis, the cases were discarded from the study. In quite a few cases, on the other hand, though clinical and Roentgen ray evidence indicated the presence of lobar pneumonia, the bacterial examination of the sputum (including passage through a mouse) and of the blood, and the white count, left the impression of an atypical virus pneumonia. These cases have, nevertheless, been included

* Aided by a grant from the Commercial Solvents Corporation, Terre Haute, Indiana.

TABLE 1.—THE EFFECT OF PENICILLIN CAPSULES R.B. ON THE TREATMENT OF PNEUMOCOCCIC LOBAR PNEUMONIA

Dosage: 200,000 Units Initially, Followed by 100,000 Units Every 3 Hours

Case	Age	Days of illness before penicillin treatment	Initial W.B.C. count	Lobe location as shown by Roentgen ray	Maximal temperature (° F.)	Hours for temperature to fall to normal	Total hours of treatment	Plasma penicillin levels in random specimens on successive days of treatment (units per cc.) Hours after previous dose of penicillin: 1	1½	2	2½	3	Remarks
1	29	2	17,500	R.U.L.	103.6	12	124	..	..	0.125	..	0.06	
												0	
										0.125	..	0.06	
								0.03	..	..	..	0.03	
2	40		25,900	R.L.L.	102.2	20	84	0.5	..	..	..	0.125	100,000 units every 4 hours after 1st day
											0.06	..	
												0.06	
								0.03					
3	36	1	14,000	R.L.L.	103.6	12	56	..	..	0.03	..	0.03	
										0.03	..	0.03	
4	38	5	8,750	L.L.L.	102.6	12	61	..	..	0.125	..	0.06	
												0.06	
												0.03	
5	25	2	44,000	R.L.	104.2	30	125	0.125	..	0.25	..	0.25	Pneumococcus found by mouse inoculation and bile test
												0.06	
												0.03	
6	33	4	12,350	L.L.L.	102.8	30	75	..	..	0.03			
										0.03			
										0.03			
7	39	2	13,700	L.L.L.	104.0	20	82	..	..	..	..	0.06	Pneumococcus found by mouse inoculation and bile test
										0.06			
8	54	2	21,100	R.L.	101.0	20	97	..	..	0.25	..	0.25	Type XIX pneumococcus found by inoculation of mouse and bile test
											0.125		
9	28	2	16,100	R.L.L.	101.4	80	156	..	..	0			
									0.03				
								0.03	..	0			
10	14	3	20,500	R.U.L.	104.2	12	106	..	..	..	..	0.06	Pneumococcus found by mouse inoculation and bile test
												0.03	
										0.03			

and, as will be seen, often showed equivocal results. The type of pneumococcus and the presence of bacteremia were not routinely determined in this series, for it was not primarily a study of pneumonia. However, in another investigation to be reported typing was carried out routinely and a correlation attempted of the type of pneumococcus with the results of penicillin treatment.

normal levels within 12 hours in 4 cases, within 20 hours in 7 cases and within 30 hours in 9 cases. Only 1 patient required treatment for more than 2 days before there was a fall to normal temperature. With the subsidence of the fever, there was also a corresponding restoration of normal pulse and respiratory rate, and this occurred in spite of the fact that the physical findings in the chest

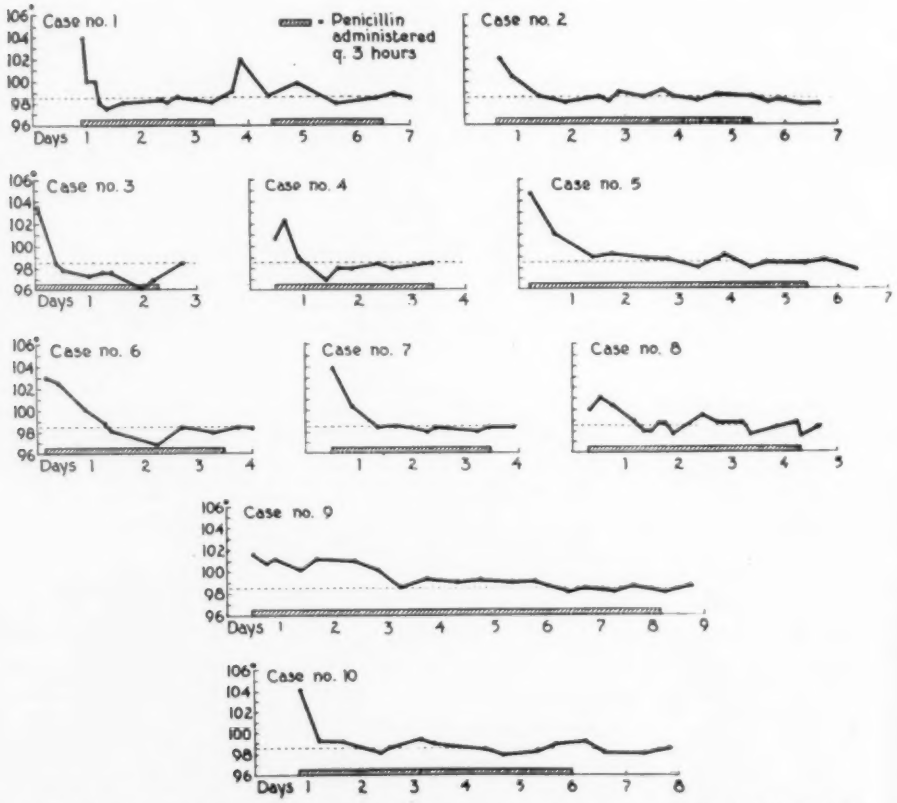

FIG. 1.—Temperature curves in 10 cases of pneumococcic pneumonia treated with penicillin Capsules R.B. (with pectin hydrolysate).

Ten patients with lobar pneumonia were treated with Capsules R.B. (These contained pectin hydrolysate as a buffer. A description of the various preparations is given in Table 1 of the previous paper.) The pertinent data in these cases are shown in Table 1 and the temperature curve in Figure 1. It can be seen that the temperature dropped to approximately

were apparently unchanged. In other words, though consolidation of the lungs was still present, the toxic symptoms had disappeared. This finding was confirmed by Roentgen ray at this state.

In several cases in this group, as in the succeeding groups, there was a secondary rise in temperature, usually on the 3rd or 4th day of penicillin treatment. The

rise was usually small (1 or 2 degrees) and was difficult to explain, since the patients were getting penicillin regularly and were showing plasma levels of 0.03 unit per cc. or higher even at 3 hours after the dose. In Case 1, the temperature rise occurred during the period of 24 hours when penicillin was omitted by mistake; the rise in this case might mean a recrudescence of the pneumococcic disease, but, in other cases, there was no such explanation possible. This secondary rise has been found to occur even in the treatment of pneumonia with parenteral penicillin.[3] The secondary rise might be explained in either 1 or 2 ways: (1) it represented a residual virus infection present along with the pneumococcic infection, or (2) it was associated with the absorption of toxic split products from the resolving consolidation in the alveoli. Whatever the explanation, such small elevations were not unlike those seen at times following the natural immunologic crisis of lobar pneumonia.

The poorest clinical results were obtained in Case 9. The temperature did not fall to the neighborhood of normal for 80 hours and even then there was a further rise during the next 16 hours. Thereafter, the patient improved rapidly, Roentgen rays taken 7 days after the initial ones showed complete resolution of the pneumonic process. The reason for the slow results in this case may be found in the plasma penicillin levels achieved. In 4 of the 6 assays, there was no measurable amount of penicillin in the blood. The plasma level was probably too low for optimal bacteriostasis. In such a case it would probably have been wise to have increased the dosage at the end of the 2nd day.

Twenty patients with lobar pneumonia were treated with Capsules No. 10 (crystalline potassium penicillin). A summary of the pertinent data is shown in Table 2 and the temperature curves are shown graphically in Figure 2, *A* and *B*. Nine of the 20 patients experienced a drop to approximately normal temperature within 24 hours. In 6 more cases, the temperature fell during the 2nd day of treatment. In the remaining 5 cases, the subsidence of the fever was slow and it was doubtful whether the penicillin did any good other than to prevent complications. In Case 53 pneumococci were never isolated and since the white count was low, the patient may have had a virus pneumonia. Case 58 was complicated by heart disease, and there was the suspicion of rheumatic fever as a further complication. It was possible that other cases showed complicating infections. In Case 64 a secondary rise in temperature occurred when penicillin was omitted by mistake for more than a day. There was a prompt fall of temperature upon renewal of penicillin medication. Yet in several other cases a secondary rise in temperature occurred even during penicillin medication as in the group treated with the penicillin buffered with pectin hydrolysate.

Another group of 10 patients with lobar pneumonia were given Tablets No. 18 (pure potassium penicillin in a high melting fat). The data in these cases are summarized in Table 3 and the temperature curves are shown in Figure 3. These patients developed pneumonia in the late winter or early spring and appeared to be much sicker than those of the previous groups who were treated in the fall. Yet 5 of these experienced a prompt subsidence of fever within 24 hours. Three others required 48 hours for the initial fall in temperature, and 2 patients required much longer treatment. In this group, the pneumococci were typed and blood cultures were made. Of the 7 cases that showed pneumococci in the sputum, 1 was of Type I, 3 of Type II, 1 of Type IV, 1 of Type VII and 1 of Type XVI. There was no determinable correlation between the type and the severity of the disease or the response to penicillin. On the other hand, all 5 cases which showed the response within 24 hours had negative blood cultures. There were 2 cases with positive cultures, 1 of Type I which required 48 hours for the return of the tem-

TABLE 2.—THE EFFECT OF PENICILLIN CAPSULES NO. 10 ON THE TREATMENT OF PNEUMOCOCCIC LOBAR PNEUMONIA
Dosage: 200,000 Units Initially, Followed by 100,000 Units Every 3 Hours

Case	Age	Days of illness before penicillin treatment	Initial W.B.C. count	Lobe location as shown by Roentgen ray	Maximal temperature (° F.)	Hours for temperature to fall to normal	Total hours of treatment	Plasma penicillin levels in random specimens on successive days of treatment (units per cc.) Hours after previous dose of penicillin: 1	1½	2	2½	3
51	42	4	17,700	R.M.I.	101.8	12	58	..	..	0.06		
52	36	4	13,650	L.L.L.	104.0	91	160	0.25		0.125 0.06 0.06		
53*	41	15	6,550	R.L.L.	104.5	183	183	0.25		0.03	0.06 0.125	
54	49	5	17,350	R.L.L.	103.2	20	108	..	..	0.06 0.03		
55	29	1	4,500	L.L.L.	101.8	20	81	0.03		0.03		
56	29	1	18,500	L.L.L.	103.0	36	144	..	..	..	..	0.03
57	3½	5	18,000	R.L.L.	102.0	20	24	..	..	0.125		
58	16	5	11,650	R.L.L. Heart disease	102.4	104	128	0.125		0.03		
59	14	4	11,450	L.L.L.	104.0	20	92	..	0.25	0.125 0.06		
60	19	4	8,500	L.L.L.	103.2	30	141	..	..	..	..	
								0.06		0.06		
61	76	4	18,900	L.L.L.	101.0	20	61	..	0.03 ..	..	0.5	
62†	65	16	10,900	R.L.L.	101.0	12	126	..	0.25 0.125			
63	25	2	36,000	R.L.L.	101.2	30	102	..	0.125 0.5			
								0.03 0.125				
64	19	4	35,000	R.L.L.	104.0	128	206	..	0.125			
								0.25	0.125 0.25 0.06 0.25			
65	22	5	7,200	L.L.L.	104.4	20	72	0.06		0.6		

64	19	4	35,000	R.L.L.	104.0	128	206	0.25	0.125 0.25 0.06 0.25	
65	22	5	7,200	L.L.L.	104.4	20	72	0.06 0.125	0.6	0.125
66	44	3	13,100	R.L.L.	103.0	39	141	0.25 0.03 0.25		0.125
67	42	5	19,950	L.L.L.	101.5	87	138	0.06 0.125	0.06	0.125
68	39	2	10,500	L.L.	103.6	41	135			
69*	48	8	13,750	R.L.	103.6	90	168	..	.. 0.5	
70	43	3	..	..	104.2	..	90	..	.. 0.03	

* Pneumococcus not isolated.
† Treated previously unsuccessfully with sulfadiazine.

TABLE 3.—THE EFFECT OF PENICILLIN TABLETS NO. 18 ON THE TREATMENT OF PNEUMOCOCCIC LOBAR PNEUMONIA

Dosage: 200,000 Units Initially, Followed by 100,000 Units Every 3 Hours

Case	Age	Days of illness before penicillin treatment	Initial W.B.C. count	Lobe location as shown by Roentgen ray	Maximal temperature (° F.)	Hours for temperature to fall to normal	Total hours of treatment	Plasma penicillin levels in random specimens on successive days of treatment (units per cc.) Hours after previous dose of penicillin: 1	1½	2	2½	3	Remarks
81	36	1	50,000	R.L.L.	101.6	24	86	..	..	..	0.03	..	Type II
82	33	4	7,600	R.M.L.	105.0	24	72	0.25	..	..	0.03	..	Type XVI
83	32	3	15,500	L.L.L.	104.2	24	96	..	0.06	..	..	..	Type VII
84	21	1	12,600	R.L.L.	102.0	10	96	0.125	..	..	0.06		
85	42	3	8,600	L.L.L.	104.0	24	168	..	..	0.06	..	..	Type IV
86	49	2	14,600	L.L.L.	102.4	24	72	..	..	..	0.06	..	Type I; blood culture positive
87	40	1	7,500	R.L.L.	100.5	48	192	..	..	0.125			
88	23	1	5,500	L. Lobes R.L.L.	103.5	192	264	..	..	..	..	0.06	Type III
89	33	7	20,400	R.M.L.	100.8	144	216	..	..	0.25	..	..	Type II; blood culture positive
90	62	4	30,200	L.L.L.	103.6	240	264	..	..	0.25			

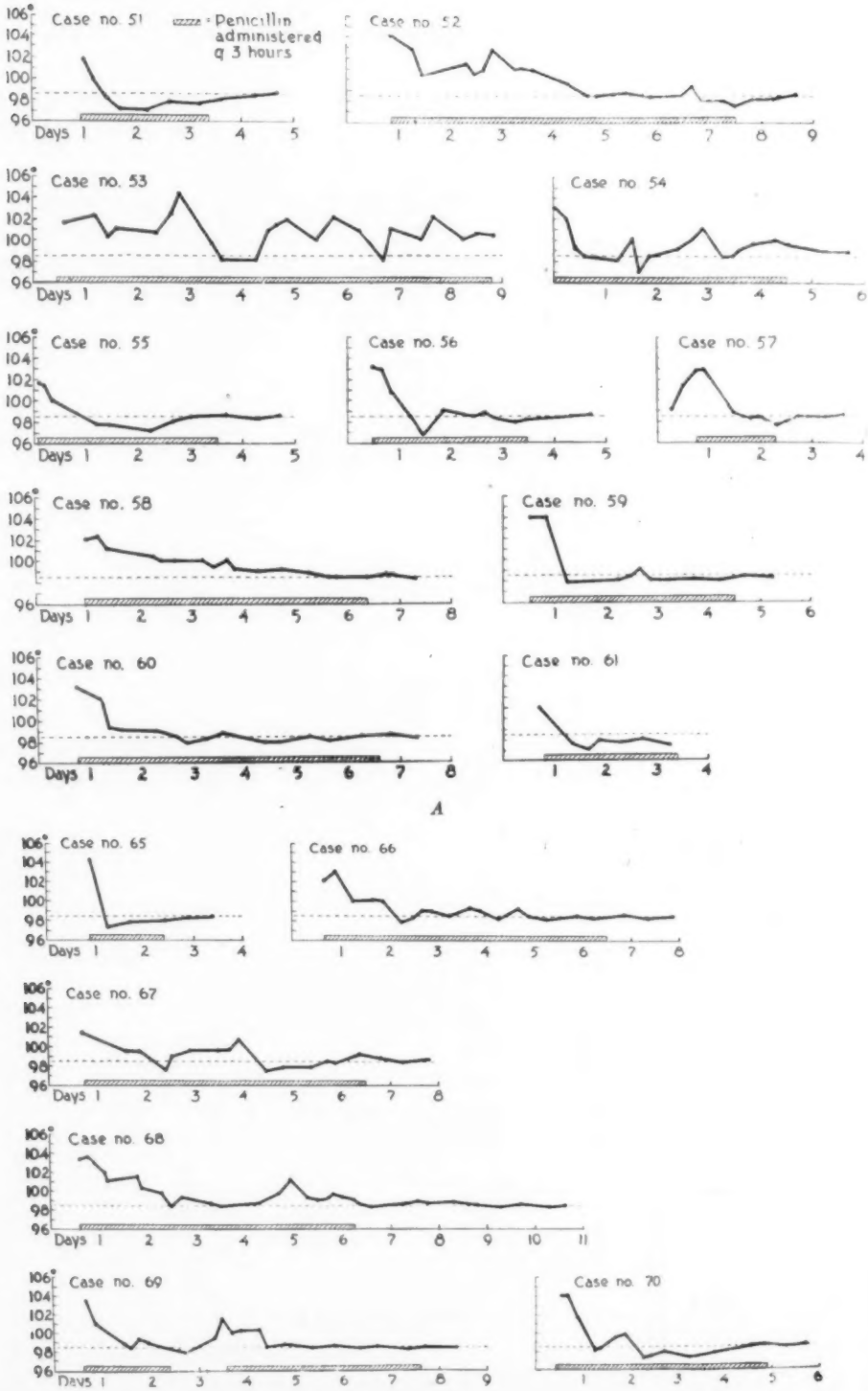

FIG. 2.—*A* and *B*. Temperature curves in 20 cases of pneumococcic pneumonia treated with Capsules No. 10 (crystalline potassium penicillin).

perature to normal, and 1 of Type II which had not responded until after 6 days of treatment. It is now well recognized that the patients showing bacteremia respond less effectively to chemotherapeutic agents.

Secondary rises in temperature occurred in several of these cases. In Case 88, the daily "spiking" of the temperature after the initial fall was suspiciously like that of an abscess, though none could be discovered. Perhaps a non-specific bronchitis (as is so frequently found in such cases) produced by a bacterium resistant to penicillin was responsible for the secondary rise in this case.

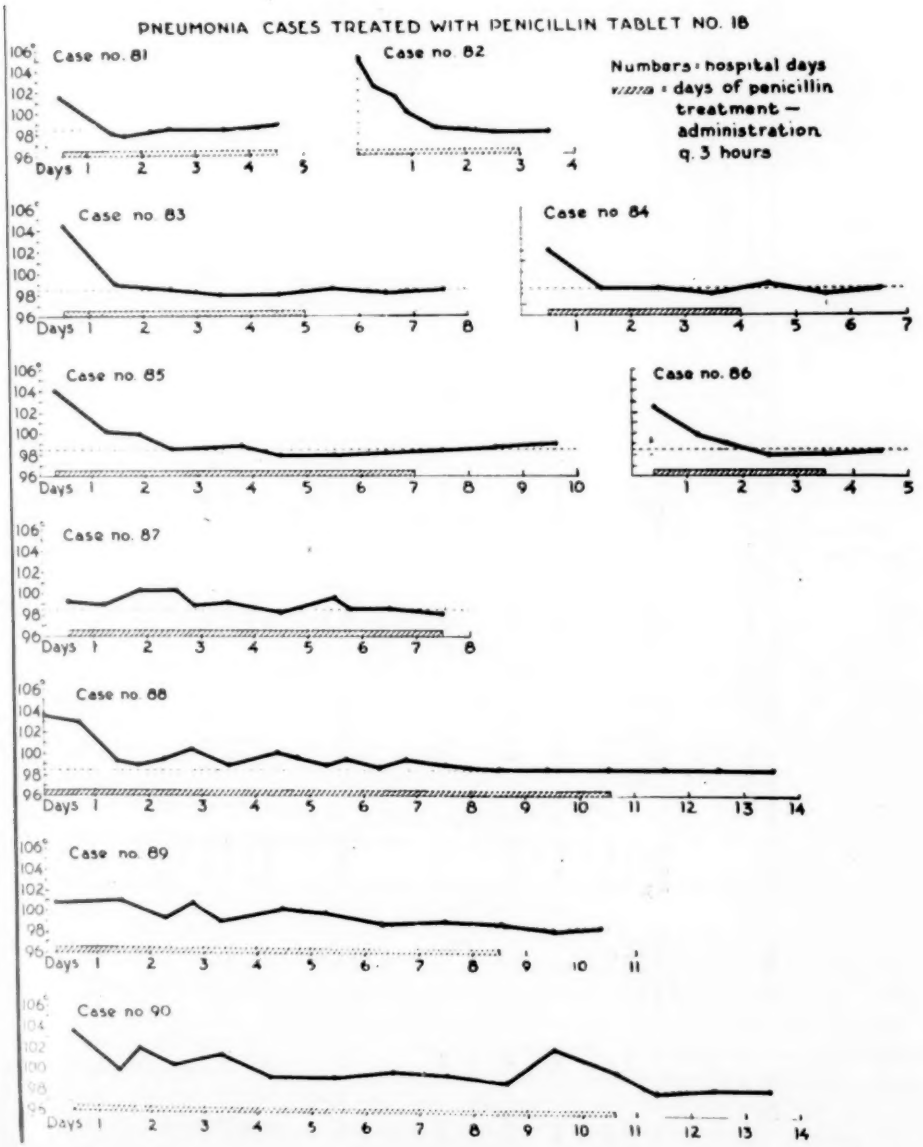

FIG. 3.—Temperature curves in 10 cases of pneumococcic pneumonia treated with Tablets No. 18 (potassium penicillin in a high melting fat).

TABLE 4.—THE EFFECT OF PENICILLIN CAPSULES C ON THE TREATMENT OF PNEUMOCOCCIC LOBAR PNEUMONIA

Dosage: 200,000 Units Initially, Followed by 100,000 Units Every 3 Hours

Case	Age	Days of illness before penicillin treatment	Initial W.B.C. count	Lobe location as shown by Roentgen ray	Maximal temperature (° F.)	Hours for temperature to fall to normal	Total hours of treatment	Plasma penicillin levels in random specimens on successive days of treatment (units per cc.) Hours after previous dose of penicillin: 1	1½	2	2½	3	Remarks
101	43	1	11,600	R.L.L.	104.2	36	140	..	..	0.25 0.25			
								0	..	0.03			
102	43	5	16,700	Bilat.	103.2	Expired	94	..	..	0.25	.. 0.06	..	Mouse inoculation neg. for pneumococcus
								1.0					
103	34	4	4,950	R.L.L.	104.2	48	179	..	..	0.25 0.06	0.125		
									0.25 0.03				
104	36	5	19,550	R.L.L.	103.6	110	209	..	..	0.5 0.25	0.125		
									0.25				
								0.06	0.25				
105	32	1	7,900	R.L.L.	102.0	133	210	.. 0	..	0.06 0.03			
								0.25	..	0 0 0.125			
106	26	1	26,000	L.L.L.	104.6	12	..	0.25					
107	17	2	11,700	L.L.L.	101.0	30	..	..	..	0.125	..	..	Type X
108	42	5	11,200	R.L.L.	102.8	30	..	..	..	0.06			
109	40	7	23,900	L.L.L.	100.8	120	..	0.125	..	..	..	..	Blood culture, positive Type II

Nine more patients were treated with the control Capsules C (crude calcium penicillin). The data for these cases are shown in Table 4 and the temperature curves in Figure 4. The 1 death in the whole series of 49 cases occurred in this group after 4 days of treatment. This patient had a bilateral pneumonia but, though the white count was 16,200, pneumococci were not isolated from the sputum or blood or from the peritoneum of a mouse inoculated with the sputum. The plasma penicillin levels were satisfactory; in fact, on the 3rd day 1 unit per cc. was achieved. This high level was probably related to the failing circulatory and renal efficiency of the patient.

Of the remaining 8 patients treated with the control capsules, 1 showed a critical fall in temperature within 12 hours, 3 more within 36 hours, 1 more in 48 hours and 3 required 5 to 6 days for a subsidence of the fever. In 1 of the 3 resistant cases (Case 109), the blood culture was known to be positive and Type II pneumococcus was isolated. In Case 104 a pneumococcus was isolated by mouse inoculation. The failure in this case to achieve good results with penicillin was difficult to understand, for 4 of 6 plasma penicillin determinations showed levels of 0.25 unit per cc. or higher. On the other hand, in Case 105, the other unsuccessful case, the failure might have been due to poor absorption

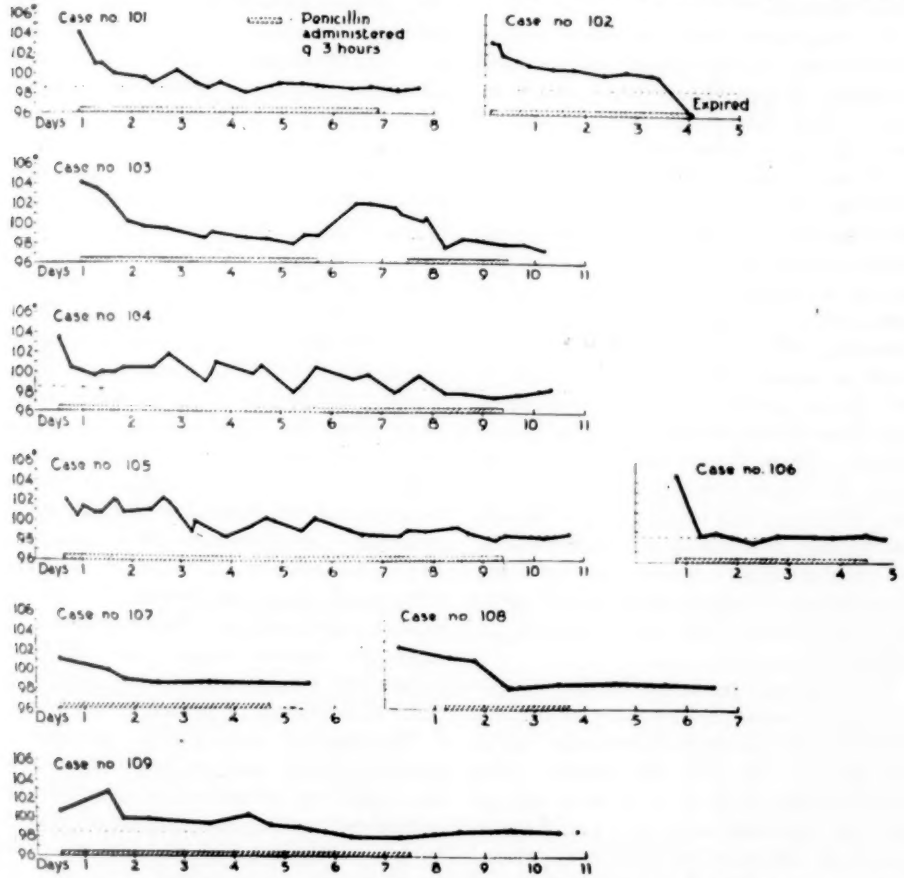

FIG. 4.—Temperature curves in 9 cases of pneumococcic pneumonia treated with Capsules C (crude calcium penicillin).

of penicillin, for 3 out of 7 determinations showed imperceptible levels and 2 others showed no higher than 0.06 unit per cc. at 2 hours after a dose. Secondary rises in temperature occurred in this group as in the others. In Case 103, it occurred after penicillin had been stopped, and promptly subsided on resumption of penicillin therapy.

In comparison with the other groups, the capsules of crude unbuffered penicillin appeared to give the poorest clinical results. Yet, the number of cases studied were too few to allow a definite conclusion to be drawn, particularly since these cases were not selected from the same epidemic of pneumonia as those of any other group. Those patients who responded to penicillin did so as promptly as those on the other preparations. Also, there were no considerable differences between the blood levels obtained with Capsules C, both in the assays and in the pneumonia cases, and those obtained with the other preparations. These facts would tend to make the 1 death and the higher percentage of poor results in this small group a fortuitous finding. If it is true that these capsules are therapeutically inferior to the other preparations of the purer forms of penicillin, the reason for the inferiority is difficult to ascertain.

The plasma penicillin levels in the 4 groups of patients were taken at varying intervals after a dose of penicillin. Usually the 9 A.M. dose was chosen. The levels ranged from 1 to 0 units per cc. but the prevailing value at 1 and 2 hours was 0.125 and at 3 hours 0.06 unit per cc., quite as was found in the assays of 100,000 units dosage after a primary dose of 200,000 units. In some of the cases in which persistently low levels were found, the clinical results seemed to be correlated with these low levels. But this was not always so, for in several cases prompt remission of fever and toxicity occurred even with low plasma penicillin levels. This is, of course, in accordance with the recognized sensitivity of most pneumococci to penicillin. In the 3 cases in which penicillin sensitivity was determined by the serial dilution method, growth of the pneumococci was inhibited in penicillin concentrations *in vitro* of 0.01 unit per cc.

Miscellaneous Infections. Table 5 gives a list of cases of miscellaneous acute infections treated with 3 of the oral preparations, namely, Capsules R.B., Capsules No. 10 and Tablets No. 18. Since it was desirable to obtain in these cases a definite bacteriologic diagnosis, the cases chosen were of necessity for the most part otolaryngologic or suppurative external lesions. The regimen was the same as in the cases of pneumonia, a primary dose of 200,000 units followed by 100,000 units every 3 hours. No perceptible difference in the clinical results could be noticed. In general, the results of the oral penicillin therapy in these cases was as good as those obtained with parenterally administered penicillin. The subsidence of fever usually occurred in 12 to 36 hours, especially when the offending organism was a *Strep. hemolyticus.* The staphylococcic infections were more resistant, as was to be expected, but the clinical response to penicillin management in these cases was easily recognizable as superior to that with purely expectant treatment. In the case of postoperative thrombophlebitis of unknown bacterial origin (Case 207), no appreciable improvement was produced until after 6 days of penicillin treatment.

The patient with acute mastoiditis associated with suppurative otitis media responded by a fall of temperature to normal within 24 hours, but she continued to have a drainage of purulent material from the ear. At the end of 15 days of oral medication, in which time the patient had ceased being toxic but continued to show drainage, the medication was changed to 30,000 units of penicillin intramuscularly every 3 hours. However, the purulent drainage persisted. By this time the organism isolated from the pus proved to be *B. proteus* rather than the streptococcus originally isolated. Thus, though oral penicillin was able to destroy the hemolytic streptococci of the mixed

TABLE 5.—THE EFFECT OF ORALLY ADMINISTERED PENICILLIN IN THE TREATMENT OF MISCELLANEOUS ACUTE INFECTIONS

Case	Age and sex	Diagnosis	Bacteria	W.B.C.	Days of illness before treatment	Maximal temperature (° F.)	Days of penicillin treatment	Hours required for temperature to fall to normal	Type of penicillin medication	Plasma penicillin levels (units per cc.) Hours after dose 1		3
201	M 26	Cellulitis, arm	*Staph. albus*	14,500	3	102.6	4	60	Capsules R.B.	..	..	0.03
202	M 60	Acute sinusitis	Pneumococcus	12,600	4	101.6	4	24	Capsules R.B.	0.06	0.06	
203	F 24	Acute pharyngitis	*Strep. hem.*	14,100	2	103.0	2	24	Capsules R.B.	..	0.125	
204	M 28	Paronychia	*Staph. albus*	11,500	4	99.6	3	24	Capsules R.B.	0.125	0.06	0.03
205	F 45	Postoper. atelectasis and bronchitis	?	12,000	2	102.4	5	36	Capsules R.B.	0.125		
206	F 26	Acute tonsillitis	*Strep. hem.*	15,200	2	101.8	5	30	Capsules R.B.	0.25	0.06	
207	F 40	Postoper. thrombophlebitis	?	16,100	2	104.0	8	144	Capsules R.B.	..	0.06	
208	M 62	Bronchitis and cardiac decompen.	?	11,500	2	100.4	4	24	Capsules R.B.	0.25 ..	.. 0.125	0.03
221	F 24	Postpartem endometritis	Mixed	15,000	4	102.6	6	36	Capsules No. 10	0.125	0.06	
222	M 34	Acute pharyngitis	*Strep. hem.*	19,100	4	101.4	4	12	Capsules No. 10	..	0.125	
223	M 46	Acute sinusitis	*Staph. aureus*	13,000	2	99.8	5	36	Capsules No. 10	0.25	0.125	
224	M 16	Acute otitis media	*Strep. hem.*	19,200	2	102.8	..	12	Capsules No. 10	0.125 0.25	0.125 ..	0.06
225	M 20	Int. laceration of leg	*Strep. hem.*	14,100	2	101.0	5	24	Capsules No. 10	0.125 0.5	.. 0.03	0.125
226	F 40	Acute bronchitis	*Staph. aureus*	13,000	4	100.2	4	36	Capsules No. 10	0.06 0.25	0.06	
227	M 25	Multiple furunculosis	*Staph. albus*	12,400	6	99.2	6	48	Capsules No. 10	..	0.06 0.125	0.03
228	M 14	Acute tonsillitis	*Strep. hem.*	16,500	2	103.0	4	24	Capsules No. 10	0.125 0.06	0.06	0.06
229	M 25	Acute pharyngitis	*Strep. hem.*	13,500	3	102.5	4	24	Capsules No. 10	..	0.125	
251	F 44	Acute mastoiditis and suppurative otitis media	*Strep. hem., B. proteus*	13,850	5	100.5	15	24	Tablets No. 18	.. 0.06	0.03 0.06 0.06 0.125	0.03
252	M 24	Acute nasopharyngitis	*Strep. hem.*	13,600	3	100.6	5	12	Tablets No. 18	..	0.03	0.03
253	M 34	Human bite of hand	*Strep. hem.*	25,300	5	100.6	8	24	Tablets No. 18	0.06	0.06	
254	M 53	Human bite of hand	*Strep. hem.*	16,700	14	99.4	7	72	Tablets No. 18	0.125 0.25	0.06 0.125	0.03
255	M 53	Infected laceration of leg	*Strep. hem., Staph. albus*	14,600	2	100.6	7	72	Tablets No. 18	0.06 0.03 0.125 0.5	0.06 0.25	0.125 0.125
256	M 44	Cellulitis of jaw	?	15,200	1	101.4	7	48	Tablets No. 18	..	0.06	
257	M 56	Acute laryngitis	*Strep. hem.*	12,400	2	99.6	5	30	Tablets No. 18	0.06	0.06	

infection, it could not, nor could parenteral penicillin, get rid of the accompanying gram negative bacilli.

Toxicity. The only toxic manifestations attributable to the oral penicillin administration was urticaria. This occurred in only 5 known instances in the 580 subjects used for assay or for therapeutic studies. Of these, 4 were relatively mild and disappeared in a day or 2; 1 lasted for 5 days and required epinephrin and antihistamine drugs. Three subjects developed urticaria with crude calcium penicillin, the remaining 2 with purified potassium penicillin. However, since both of these latter patients had previously been given sulfonamide medication and especially since the skin involvement was atypical, their reaction might have been due to the sulfonamide. In 1 instance, the reaction occurred on the 2nd day of administration; in 3 it occurred after the medication was completed, on the 6th or 7th day. In the 5th subject, urticaria occurred 2 weeks after treatment when the patient was given several more tablets for a recurrence of the symptoms of sinusitis.

The total incidence of urticaria is 0.86%, if the assay subjects are included. It is 3.8% if only the 130 therapeutic cases are counted. The incidence is only 1.5% (and these may be spurious cases) in the patients treated with purified preparations of penicillin. These values indicate a lower incidence of skin reactions than the 5.7% reported by Lyons[4] or the 5.5% by Rostenberg[5] for parenterally injected penicillin. The low incidence may be due to the oral route or to a less antigenic potentiality of purified preparations of penicillin. The latter appears to be the case, since in a study of purified preparations given parenterally[1] no urticarial reactions were encountered.

Discussion. The most obvious conclusion from these studies is that orally administered penicillin is therapeutically successful even in serious infections, if a sufficiently high dose is given. This dose is higher than the 25,000 or 50,000 units recommended in the package descriptions found with the commercially available oral penicillin. Such doses, even at 2 hour intervals will not produce more than 0.06 unit per cc. most of the time, and may frequently yield only 0.03 unit or less per cc. On the other hand, 100,000 units, especially after an initial "booster" dose of 200,000 units tend to produce 0.125 unit or more per cc. for at least 2 hours and most often 0.06 unit in the 3rd (and sometimes 4th) hour. Such levels should be effective against infections by most of the organisms regarded as sensitive to penicillin.

The clinical results in 49 cases of pneumonia and 81 cases of miscellaneous infections bear out this impression. In 77% of the cases of pneumonia, subsidence of fever and toxic symptoms occurred within 48 hours. Many of these patients actually showed a critical drop in temperature during the first 12 hours, a result as good as any obtained with parenterally injected penicillin. Of the remaining 23%, some had complicating involvements due to virus or penicillin-resistant bacterial infections. Similar results were found in the miscellaneous group, especially when the organism involved was a *Strep. hemolyticus.* Staphylococci infections were usually more resistant but even these responded satisfactorily to oral penicillin.

Since it has been demonstrated that the large majority of patients with acute infections treated orally with penicillin show subsidence of fever and toxic symptoms within 48 hours, failure to achieve such successful therapeutic effect in that period should be the signal for immediate reinvestigation of the clinical features of the case. The reason for failure may be one of the following: 1. Penicillin has been inadequately absorbed or its administration for other reasons has unexpectedly produced low plasma concentration. This phenomenon occurred in a few of our cases.

2. The illness has not been due to a penicillin-sensitive organism. For example, pneumococcic pneumonia may be simulated by a virus pneumonia.

3. The bacterium involved may be an

unusually resistant strain of what is normally a penicillin-sensitive microörganism.

4. There may be a complication much more difficult to treat than the primary infection. In cases of pneumonia, especially in elderly persons, an accompanying severe bronchitis with a thick tenacious mucopurulent exudation, may require very high concentrations of penicillin for successful management.

If any of these 4 factors are present, the original dose of penicillin will prove to be inadequate. It is recommended, then, if after 48 hours of oral treatment with penicillin no subsidence of fever and toxicity has occurred, that the dosage be doubled or that parenterally administered penicillin be given in doses of 40,000 or 50,000 units every 3 hours. In the meantime the patient should be carefully reexamined for complications, and, at the same time, the offending bacterium should be isolated and tested for penicillin sensitivity. Even if the disease process turns out to be due to a virus infection, the additional penicillin will at least have served to prevent or minimize complications.

The severity of the infection has no relation to the resistance of the offending organism to penicillin. The most serious cases of pneumonia may be produced by pneumococci the growth of which is inhibited by very low concentrations of penicillin. These will usually respond rapidly to the recommended doses of penicillin. On the other hand, mild infections due to a staphylococcus, such as paronychiæ or furuncles, may require very much higher doses of penicillin than needed for a severe streptococcus sore throat. Similarly, bronchitis due to staphylococci may be much more difficult to treat than lobar pneumonia. Thus, the general recommendation of small doses of penicillin orally, say 25,000 or 50,000 units, for mild infections is fallacious. The criterion for dosage should be only the sensitivity of the organism to penicillin. It would be safer to make the general recommendation of the dosage used in this study, namely, 200,000 units initially followed by 100,000 units every 3 or 4 hours. Our most recent experience indicates that after the critical fall in temperature has occurred there is probably little danger in giving 200,000 units for the 8 hour sleep period and returning to 100,000 units every 4 hours for the remaining period of the day.

Summary. 1. Forty-nine patients with pneumococcic lobar pneumonia and 81 patients with miscellaneous infections produced by penicillin-sensitive organisms were treated with several preparations of penicillin orally administered in primary doses of 200,000 units followed by 100,000 units every 3 hours.

2. In 77% of the cases of pneumonia, subsidence of fever and toxic symptoms occurred within 48 hours, some within 12 hours. Of the remaining 23%, failure was due to (*a*) inadequate absorption of penicillin, (*b*) the presence of a penicillin-insensitive organism such as a virus, (*c*) penicillin-resistant pneumococci, or (*d*) overwhelming complications.

3. The patients with miscellaneous infections responded similarly well to oral management with penicillin, those with hemolytic streptococci rapidly and those with staphylococci more slowly. The results were comparable with our experience with parenterally administered penicillin.

4. The plasma penicillin levels under this regimen were usually 0.06 unit per cc. or higher during most of the 3 hour interval between doses, as had been anticipated from assays.

5. Urticaria occurred in 3.8% of the 130 therapeutic cases and only in 0.86% of the 580 total subjects used for either assay or treatment. When purified preparations were used, only 2 spurious cases of urticaria developed.

6. The severity of the infection has been found to have no relation to the penicillin dosage required. Only the sensitivity of the organism to penicillin should be the determining factor in dosage.

7. Crude calcium penicillin in capsules gave the poorest therapeutic results. For the other preparations used, there was no considerable difference in the results obtained.

The authors wish to acknowledge their indebtedness to Mrs. Ellen Zimmermann, Mrs. Marion McCoy Miss Kathleen O'Donnell and Miss Margaret Casella for their technical assistance.

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THE SEROLOGIC RESPONSE FOLLOWING PENICILLIN THERAPY FOR EARLY SYPHILIS*†

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The evaluation of a new antisyphilitic agent is an arduous time-consuming, and painstaking procedure. Before clinical trial in human infection is justified the drug must have been demonstrated in the laboratory to be both therapeutically efficacious and nontoxic. In the final analysis, therapeutic efficacy is measured in human infection in terms of clinical and serologic cure. This is determined in early syphilis by the absence of relapse (clinical and/or serologic), of seroresistance, and of late progression in large numbers of patients followed after termination of treatment for prolonged periods, probably a minimum of 5 years.[12] There are, however, in early syphilis immediate indicators of therapeutic adequacy which permit preliminary evaluation in shorter periods of time: the disappearance time of *T. pallida* from superficial lesions, the rapidity of healing of early manifestations, the serologic response measured by quantitative methods, and the outcome of pregnancy in syphilitic females.

Since the original demonstration of the treponemicidal action of penicillin by Mahoney, Arnold, and Harris,[7] much has been accomplished through cooperative effort[10-14] toward the evaluation of this new chemotherapeutic agent in syphilis. In this instance, because of the urgency of war and the almost complete absence of toxicity, clinical trial in man has proceeded simultaneously with experimental trial in the laboratory. The rapidity of disappearance of surface organisms and of healing of visible lesions compares favorably with previously used therapeutic agents. Preliminary reports[10,8,1] suggest that the initial serologic response is satisfactory, but data comparing the serologic response following penicillin therapy with that under previously established methods of treatment have not yet been presented. It is the purpose of this report to provide information with respect to this pertinent point.

Material and Method. The distribution by race, sex, and age of the 208 patients comprising this material is indicated in Table 1. Only patients presenting previously untreated primary or secondary syphilis who submitted to hospitalization for treatment with penicillin between Sept. 28, 1943 and Dec. 1, 1945 are considered in this report. The diagnosis was confirmed in each instance by darkfield demonstration of *T. pallida*. Additional studies performed on each patient before

* The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Washington University.

† The Chairman of the Advisory Committee to the National Institute of Health Syphilis Study Section has suggested that publications of the cooperative study of penicillin in syphilis be prefaced by the following statement: "The results which are to be presented in this paper must be interpreted in light of the fact that from June 1943, the date of inception of the study, to the present, commercial penicillin has been a changing mixture of various substances. The content of "impurities" has gradually decreased as potency, in terms of units per mgm., has increased. The relative amounts of the several identified penicillin fractions G, F, X, and K, have likewise varied from time to time. Those two changes, and perhaps others, suggest that therapeutic efficacy may not have remained constant; and that it may be significantly different today than it was originally. It is not now possible to assess the extent to which these changes may have affected the results here reported."[9]

treatment included a quantitative blood serologic test for syphilis (Kahn) and an examination of the cerebrospinal fluid (cell count, total protein determination, colloidal test, and Kolmer Wassermann). Penicillin was administered to approximately 90% of the patients in this series by one of the 3 following schedules: (1) 1.2 million Oxford units (total dosage) in $3\frac{3}{4}$ days (51 patients), (2) 1.6 million units in 10 days (73 patients), and (3) 4.8 million units in $7\frac{1}{2}$ days (58 patients).* The sodium salt was employed exclusively, equally divided doses being injected intramuscularly every 3 hours.†

from consideration when either clinical relapse, or the initial evidence of a subsequently confirmed serorelapse occurred.

Data collected in this manner are presented to show: (1) the serologic response following penicillin in comparison with that during the first 8 weeks of prolonged weekly arsenical and bismuth therapy and, (2) the serologic response following penicillin therapy during the first year after treatment according to duration of disease, race, sex, age, and outcome of pre-treatment spinal fluid examination.

For the comparisons, 2 studies were selected from the literature which illustrate

TABLE 1.—DISTRIBUTION OF 208 PATIENTS WITH EARLY SYPHILIS BY RACE, SEX, AND AGE

Age (years)	Negro		White		Total
	Males	Females	Males	Females	
Under 20	13	33	1	6	53
20–24	14	20	10	20	64
25–34	23	9	20	16	68
35 and over	8	1	6	8	23
Total	58	63	37	50	208

After completion of therapy, patients were instructed to return at semi-monthly intervals for the initial 3 months and monthly thereafter during the first year of post-treatment observation. Clinical and quantitative serologic examinations were performed on each return visit. The quantitative blood serologic titer was determined by the Kahn technique and recorded in Kahn units.[6]‡ For the purpose of this study patients were withdrawn

the serologic response during the first 8 weeks of arsenical therapy administered by prolonged methods (weekly injections). In one of these, Moore, Stanton, Robinson, and Eagle[11] present the serologic responses observed during therapy with five different arsenical drugs (arsphenamine, neoarsphenamine, silver arsphenamine, bismarsen, and mapharsen) in terms of average subsequent titers§ as compared with pre-treatment titers. In the other, Crosby and

* The remaining 10% were treated over similar time-periods but with varying total dosages.

† The relatively small number of patients treated by these several methods preclude in this report a study of the effect of individual schedules. In the cooperative study,[10] no difference was noted in the serologic response with total dosages varying from 300,000 to 1.2 million units; with 60,000 units the rate of fall of serum reagin appeared to be retarded.

‡ This method of quantitation, as described by Kahn and as used in this study, is as follows: "A definitive precipitate (+ + + +, + + +, or + +) is recorded as positive, while a very weak reaction is discounted. If a serum gives a + + + +, + + +, or + + reaction in an undiluted state only and is negative in the dilution series, it is considered as containing Kahn units as indicated by the plus-signs (4 units, 3 units, or 2 units respectively). The potency of any serum which is positive on dilution is determined according to the formula $S = 4\ D$, where S is the serum potency in terms of Kahn units and D is the highest dilution ratio giving a positive (+ + + +, + + +, or + +) reaction. Thus if serum dilution 1:5 is positive and 1:10 and higher dilutions are negative, the serum contains 5 x 4 or 20 Kahn units."

§ In this method of analysis, the average (mean) pre-treatment titer is assigned the value of 100, and at each subsequent observation the average titer is expressed in terms of per cent of the original. The quantitative method used by Moore et al. was a complement-fixation technique, results being expressed in dilution units.

Campbell[2] used median titers* to portray the serologic response of patients during weekly treatment with the arsenicals (without distinction between the several drugs) according to the stage of disease at onset of treatment.

The latter method is used also in the second part of this paper to demonstrate the serologic response during the first year following penicillin therapy.

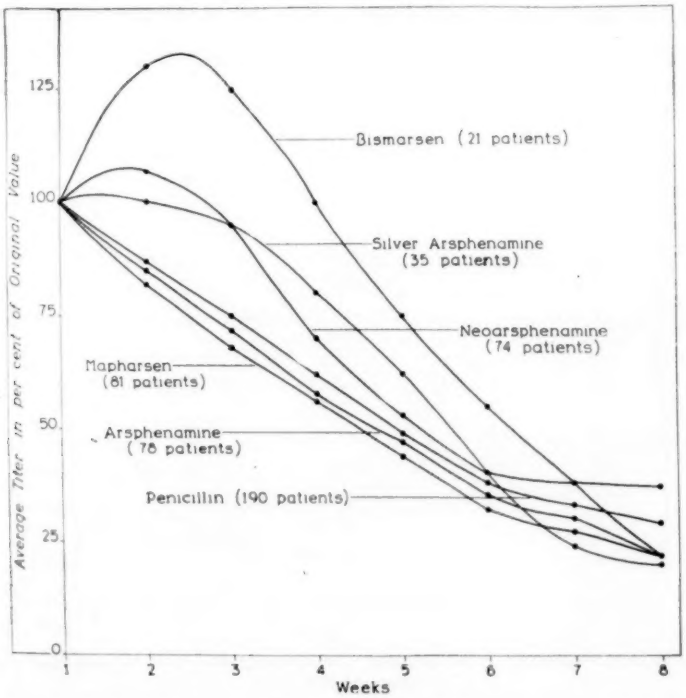

FIG. 1.—Comparison of serologic response in early syphilis during treatment with the arsenicals and following penicillin. (After Moore, Stanton, Robinson and Eagle, Am. J. Syph. Gonor. and Ven. Dis., courtesy of C. V. Mosby Co.)

1. *Comparison of Serologic Response During the First Eight Weeks of Arsenical Therapy and Following Penicillin.*

(*a*) *With Different Arsenical Drugs.* The number of patients treated with each of five drugs and the observed serologic trends are indicated in Fig. 1, taken from the first report,[11] of 289 patients with seropositive primary or early secondary syphilis during weekly treatment. Superimposed on this graph is the result following penicillin therapy in 190 patients in the same diagnostic categories. It is clear that the rates of fall of serum reagin during weekly treatment with the arsphenamines (old arsphenamine, neoarsphenamine, silver arsphenamine, bismarsen) and with arsenoxide (mapharsen) are essentially similar, and that, by this method of comparison, the serologic response following penicillin therapy over this time-period does not differ materially from the other agents.

(*b*) *By Stage of Disease.* In Figs. 2–4 the serologic response following penicillin therapy is compared with the results

* Medians are used rather than the averages (means), since these values, above and below which there are an equal number of observations, give a more representative description, not being thrown far in one direction or the other by extremely high or low observations. These median values are plotted on arithlog paper in order to portray the *rate* of change of one line in respect to others.

depicted by Crosby and Campbell[2] in their study of patients according to stage of disease.

A comparison of the serologic response in seropositive primary syphilis during the first 8 weeks of arsenical treatment and that following penicillin therapy is shown in Fig. 2. The median pretreatment complement-fixation dilution titer (120) is considerably higher than the corresponding Kahn titer (40), but at the end of 4 weeks the figures are identical and in the penicillin treated patients becomes accelerated and the trends for the last two weeks are similar.

A delay in the rate of fall of serum reagin following penicillin therapy appears even more pronounced in patients with late secondary syphilis* (Fig. 4). Although before treatment the median titers were identical, at the end of 8 weeks the median titer of the penicillin treated group has declined only 50% as compared to an 85% fall in the arsenical treated patients.

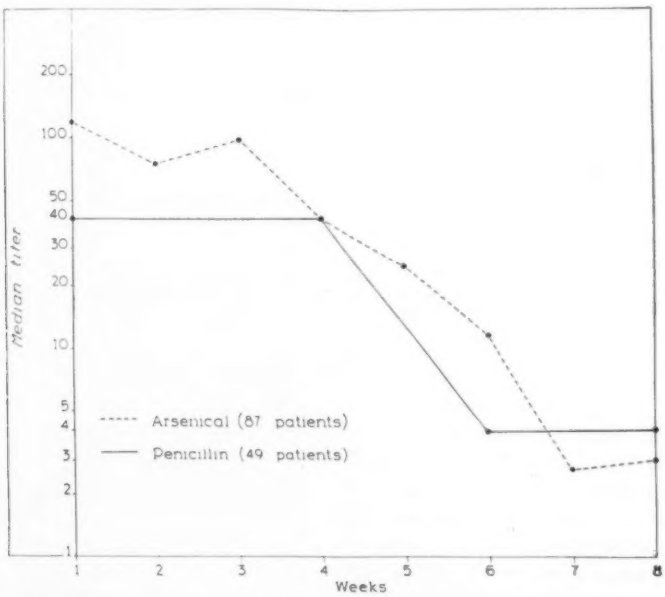

FIG. 2.—The serologic response in seropositive primary syphilis result of penicillin compared with arsenical therapy.

remain essentially the same through the 8th week. The over-all serologic trends of the two treatment methods suggest that, in this comparison, the response following penicillin may be slightly less prompt over this time-period than that recorded during arsenical treatment.

In early secondary syphilis* (Fig. 3) the rate of fall of serum reagin following penicillin therapy appears to be retarded initially in comparison with that during treatment with the arsenicals. After the 6th week, however, the serologic response The significance of these comparative trends is discussed in a subsequent paragraph.

2. *Serologic Response During the First Year Following Penicillin Therapy for Early Syphilis.*

(*a*) *By Stage of Disease.* For the purpose of comparison with arsenical therapy the foregoing graphs depicted the results of only the first 8 weeks following penicillin therapy. The eventual serologic outcome of the penicillin treated patients in relation to stage of disease at the onset of

* Secondary syphilis has been divided arbitrarily into early (duration of secondary lesions 21 days or less) and late (duration of secondary lesions 22 days or more).

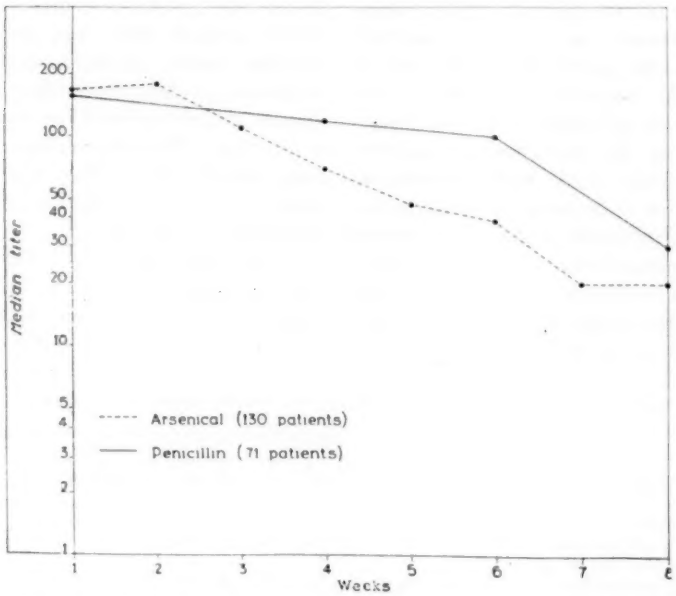

FIG. 3.—The serologic response in early secondary syphilis* result of penicillin compared with arsenical therapy.

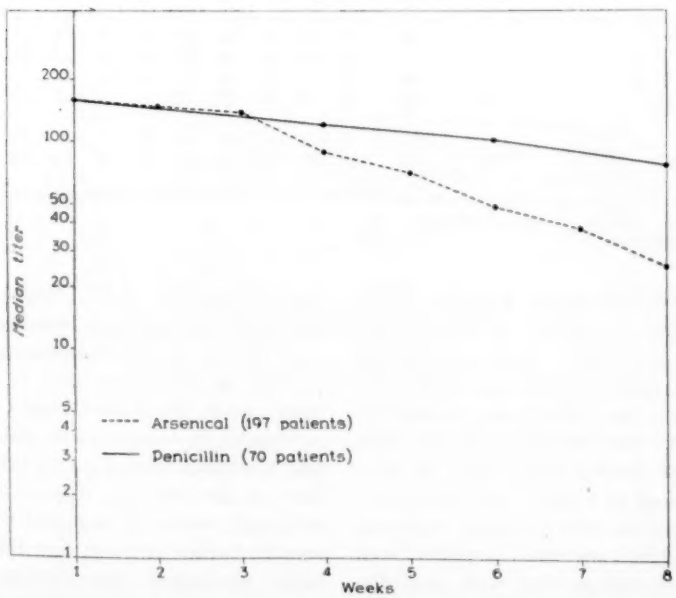

FIG. 4.—The serologic response in late secondary syphilis† result of penicillin compared with arsenica therapy.

* Early secondary syphilis—duration of secondary lesions 21 days or less.
† Late secondary syphilis—duration of secondary lesions 22 days or more.

treatment is shown in Fig. 5. (The number of observations on which this and the following graphs are based is indicated in Table 2). As depicted in the graph, the serologic trends, as indicated by the degree of declivity of the lines, for seropositive primary syphilis and early secondary syphilis appear to be roughly parallel, the median pre-treatment Kahn titers being 40 and 160 respectively, while the interval between the beginning of treatment and permanent seronegativity was 16 weeks for seropositive primary syphilis and 24 weeks for early secondary syphilis. With late secondary syphilis, although the median pre-treatment titer corresponds with that of early secondary syphilis, the decline of titer was slower, and permanent seronegativity was delayed until the 36th week. These results correspond, in general, with those of Crosby and Campbell. In their material, the serologic response for seropositive primary syphilis was accelerated in comparison with that for early secondary syphilis. Between early and late secondary syphilis the delay in the serologic response of the latter was less evident than in the present material. In the light of these combined results, it would appear that the time interval between onset of treatment and seronegativity is dependent upon duration of disease as well as upon the original height of the titer. This observation corresponds with clinical experience, the longer the duration of disease, the longer the period to serologic negativity.

(*b*) *By Race and Sex.* The modifying effect of race and sex on the course of syphilitic infection is too well known to require documentation. The propensity for late syphilis in the Negro to involve the cardiovascular and osseous systems in contrast to the predominance of neurosyphilis in the white race is well recognized, as is the milder course of syphilis in females as compared to males. Crosby and Campbell found no significant difference in the serologic response during the first eight weeks of arsenical treatment in respect to race and sex, but did not report more prolonged observations. In the present study, however, it is possible to determine eventual serologic tendencies, as shown in Fig. 6. No marked difference is apparent in the serologic response be-

TABLE 2.—NUMBER OF OBSERVATIONS ON WHICH GRAPHS ARE BASED*

Fig. No.	Indicating	No. of Patients	No. of Initial Observa.	No. of Post-treatment Observations in Follow-up Period Terminating at 4 wks.	8 wks.	12 wks.	16 wks.	20 wks.	24 wks.	28 wks.	32 wks.	36 wks.	40 wks.	44 wks.	48 wks.
5	*Stage of Disease*														
	Seropos. prim. syphilis	49	49	26	56	55	30	22	23	21	16	15	9	11	10
	Sec. syphilis—duration 21 days and under	71	66	25	91	58	39	35	31	28	27	17	18	17	14
	Sec. syphilis—duration 22 days and over	70	66	23	79	60	43	32	28	17	15	14	15	14	10
6	*Race and Sex*														
	C M	58	56	25	68	54	32	18	21	15	13	12	9	12	9
	C F	63	61	18	74	58	36	38	36	25	22	18	17	14	14
	W M	37	36	13	47	32	21	15	8	14	9	8	5	8	7
	W F	50	49	24	60	41	25	28	23	18	20	15	13	14	11
7	*Age Group*														
	Under 20	53	50	13	61	45	30	27	26	19	14	13	9	12	9
	20–24	64	61	25	73	64	30	28	26	22	19	15	12	12	7
	25–34	68	68	32	86	63	36	32	24	24	24	16	16	15	20
	35 and over	23	23	10	30	18	17	12	11	8	7	7	8	9	5
8	*CSF*†														
	Normal	143	137	46	158	133	84	67	54	45	38	29	28	27	25
	Abnormal	62	57	34	79	53	28	28	30	27	24	18	15	20	13

* The presence in certain of the follow-up periods of more observations than of original patients is due to multiple visits by the same patients.

† Cerebrospinal fluid.

tween males and females of the white race, and the trend in Negro male patients does not differ significantly from that of white males. It is true that the median pre-treatment titer of white females was higher than either of the male groups and

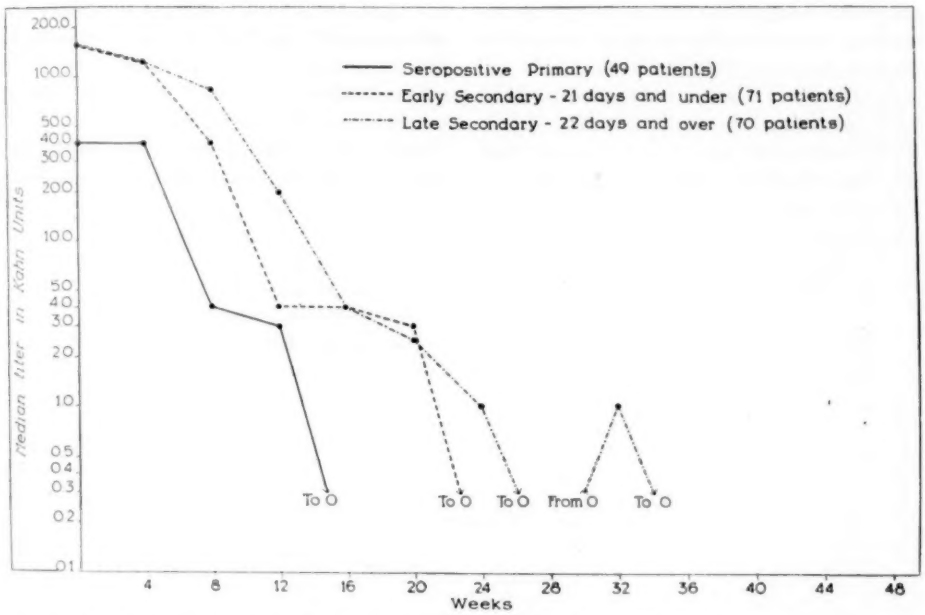

FIG. 5.—Serologic response following penicillin therapy for early syphilis by stage of disease.

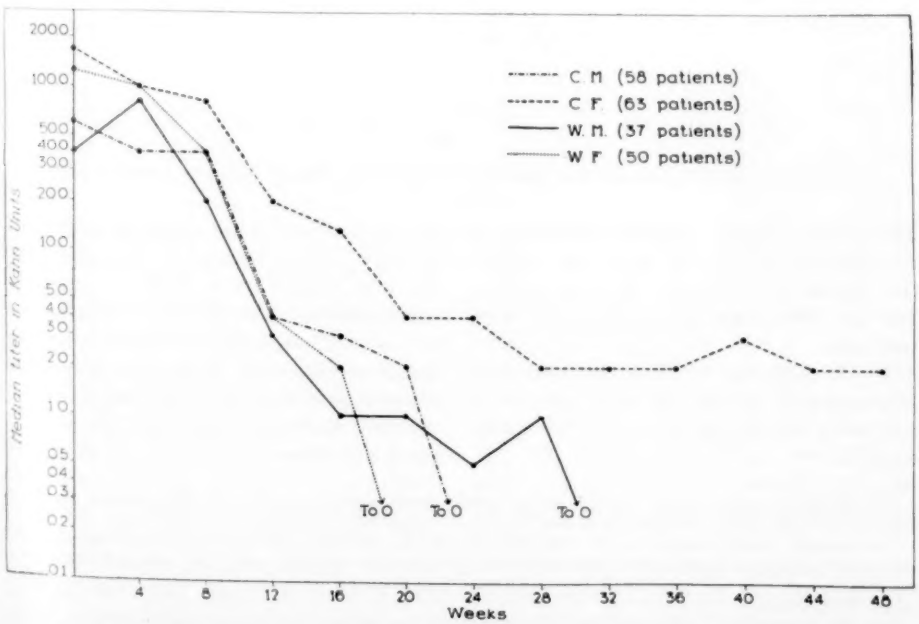

FIG. 6.—Serologic response following penicillin therapy for early syphilis by race and sex.

that the former attained seronegativity more promptly than either of the latter. However, the striking feature of this graph is the retarded rate of fall of serum reagin in Negro females, this group remaining seroresistant through the 48th week of post-treatment observation.*

(*c*) *By Age.* The serologic trends of the four age groups (under 20, 20–24, 25–34, and 35 and over) into which this material has been divided is portrayed in Fig. 7.

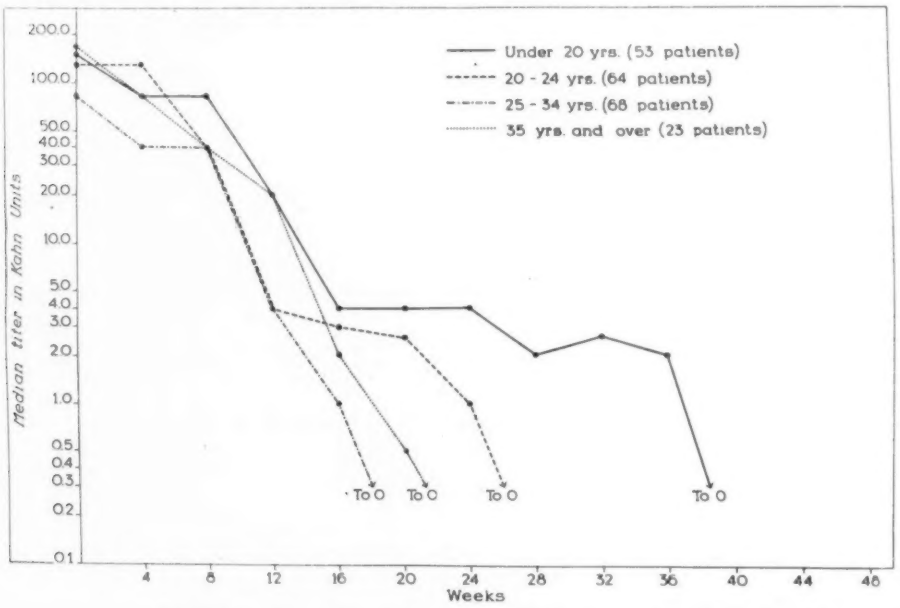

FIG. 7.—Serologic response following penicillin therapy for early syphilis by age.

The most prompt serologic response is recorded in the 25–34 years age group, the slowest in the under 20 years group, and the remaining two groups are intermediate.

3. *The Influence of Early Asymptomatic Neurosyphilis on the Serologic Response Following Penicillin Therapy for Early Syphilis.*

The blood serologic response of patients with normal and with abnormal pretreatment spinal fluids† is presented in Fig. 8. Although the initial response of the patients with early asymptomatic neurosyphilis appears slightly retarded, this is probably not significant since the over-all trends are identical. This observation is in agreement with the study of Crosby and Campbell, who found no difference in blood serologic response during the first 8 weeks of arsenical treatment between 30 patients with abnormal and 496 with normal spinal fluids.‡

Discussion. The difference in the statistical methods used may account for the apparent disparity in results when our material is compared with that of Moore, Stanton, Robinson, and Eagle on the one hand and when it is compared with that

* It should be pointed out that the serum reagin level persisting from the 28th through the 48th week (2–3 Kahn units) corresponds to the "doubtful" range with qualitative serodiagnostic tests.

† Arbitrarily, cerebrospinal fluids with any one of the following changes have been classified as abnormal—cells over 6 per cubic millimeter, total protein over 40 mgms. per cent, colloidal test with a reading of over 2 in any tube, complement-fixation test doubtful or positive in maximum amounts of spinal fluid or less.

‡Fluids were tested after 6 months of treatment rather than prior to treatment as in the present study.

of Crosby and Campbell on the other. In the former (according to drug used), the serologic trends appear to be essentially similar, while in the latter, compared by stage of disease, there is an apparent retardation in the serologic response following penicillin. Moore *et al.*, using mean (average) values, assigned arbitrarily the value of 100 to the mean pretreatment titer and computed subsequent titers in terms of per cent of the original. These results were plotted on arithmetic graph paper. The method of Crosby and Campbell used median rather than mean titers, these being plotted directly on arithlog graph paper. The former statistical method may be preferable for the purpose of comparing trends of different tests since it is less affected by serologic vagaries, although it has all the disadvantages of the use of averages rather than of medians as centering values. The chief advantage is the common starting point of the trend lines. The use of percentages of this value for subsequent points plotted on arithmetic graph paper accomplishes the same purpose as the use of arithlog graph paper for actual values. In any graphic comparison of serologic trends it must be remembered that the actual rate of fall (the degree of declivity of the lines) is *predetermined* to a large extent by the dilutions of the serum routinely tested by whatever quantitative technique employed. For example, if a quantitative test is performed on serially two-fold diluted serum (this is the procedure usually followed), unless interpolation is performed, the reagin titer of each successive tube can be only 100% greater than the preceding one (4, 8, 16, 32, etc.); and conversely, decreasing titer can only be 50% if slight (one tube), 75% if greater (two tubes), and 87.5% (three tubes) etc. (32, 16, 8, 4, etc.). Thus, under these circumstances, only gross comparisons can be made, since slight differences are not apparent.

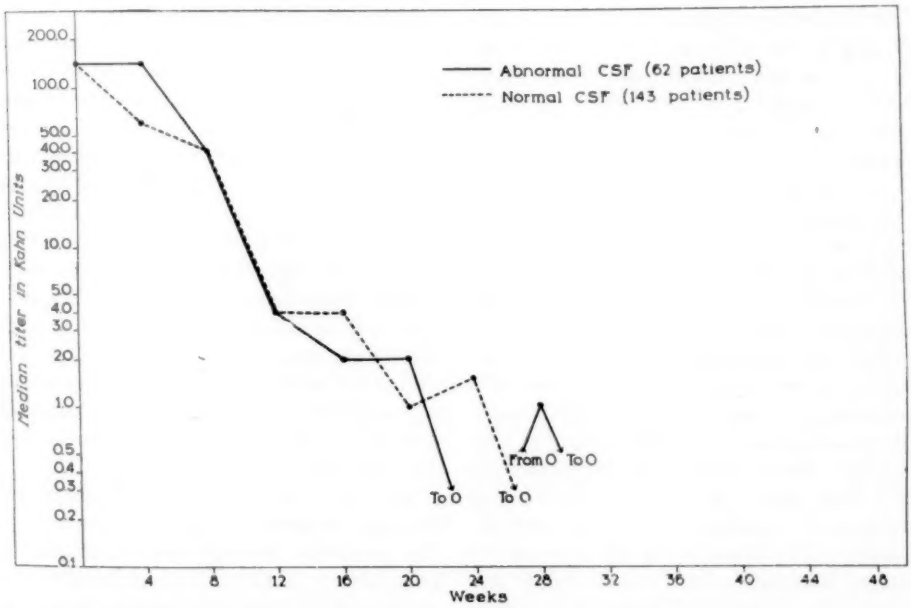

FIG. 8.—Serologic response following penicillin therapy for early syphilis effect of early asymptomatic neurosyphillis.

There are 3 other technical factors which render difficult comparisons of serologic results: (1) variations in sensitivity of the tests; (2) differences in

methods of reporting results (units); and (3) differences in interpretation of degree of positivity (defining the end-point in quantitative techniques).

The importance of variations in sensitivity which are inherent in all serologic tests for syphilis, although recognized by serologists and syphilologists alike, cannot be too repeatedly emphasized. This factor obtains not only in comparisons between two different serologic techniques (one flocculation as compared with a second flocculation test; or, a complement-fixation technique as compared to a flocculation test) but also when the same technique is performed in two different laboratories, and, because of unavoidable day to day variation in sensitivity, even when the same technique is performed in a single laboratory.

In the present study, a quantitative flocculation technique was employed in contrast to the quantitative complement-fixation procedure used by Crosby and Campbell. The latter technique, although inherently more sensitive than the flocculation test, is *less* sensitive than the former in sera of low reagin content because of a constituent of serum which inhibits complement-fixation in low dilutions.[3] In sera of high reagin content (high-titered), on the other hand, the effect of this serum inhibitor is nullified by dilution and the resulting (by dilution) small amounts of reagin remaining are more readily detected by complement-fixation techniques. Therefore, titers determined by complement-fixation methods under such conditions are higher than with flocculation techniques. Considering this factor alone (*i.e.*, disregarding the Kahn method of expressing units of serum reagin in multiples of the dilution) it would be anticipated that the pre-treatment titers obtained by Crosby and Campbell in general would be higher* and the serologic decline more precipitous than in the present study.

The second factor affecting the present comparisons is the differing methods of reporting units of serum reagin. Crosby and Campbell expressed the quantitative titer in *dilution units*† while in the present study results are expressed in *Kahn units* (approximately four-fold greater than dilution units‡). This factor considered alone would tend to make the original titer higher in our material. This difficulty could be eliminated if serologists would uniformly express quantitative results in dilution units, a standard practice in reporting results of other serum tests of antigen-antibody reactions.

The third technical factor is concerned with the definition of the end-point in quantitative techniques. In the Kahn technique (the present study) 2+ is read as positive[6] whereas in the complement-fixation technique of Crosby and Campbell's study 2+ was considered as doubtful.[4] The total influences of these factors (complement-fixation *vs.* flocculation technique, dilution units *vs.* Kahn units, and the varying definitions of the end-point) on comparisons of serologic response are difficult of evaluation. The interpretation of comparative trends, therefore, must be considered in the light of these indicated complexities.

In view of the correlation between the serologic response in early syphilis following penicillin therapy and that during treatment with the several arsenical drugs reported by Moore, *et al.*, it would appear that, with any effective treatment method (or drug) the rate of fall of serum reagin is essentially constant. Since, as pointed out by the previous authors in reference to the arsenicals, these several antisyphilitic agents are not equally therapeutically efficacious as judged by ultimate clinical outcome, it is apparent that the quantitatively measured serologic response, while of value, is not an important criterion of therapeutic efficacy.

* Except in low-titered seropositive primary syphilis.

† With this method, serologic titer is expressed in terms of units of reagin corresponding to serum dilution. Thus, if a given serum is positive in a dilution of 1:2 (1 part of serum and 1 part of isotonic saline) and negative in higher dilutions, it is said to contain 2 units of reagin. Similarly, if positive in a dilution of 1–100 but negative with higher amounts, it is said to contain 100 units, etc.

‡ See footnote page 356.

Another consideration in comparative studies of serologic response following treatment for early syphilis is the similarity of the basic material. Comparisons are not valid unless there is a similar distribution of patients by stage (duration) of disease. The effect of duration of infection in early syphilis on ultimate clinical outcome has been emphasized recently by Eagle[5] and confirmed by the Penicillin Panel[10] who, in contrast to previous observers,[13] found an increased incidence of relapse in secondary as compared to seropositive primary syphilis.

Table 3.—Important Variables According to Stage of Disease

Stage of Disease	Number of Patients	Abnormal CSF Per cent With	Duration of Treatment (Days) Per cent in 3¾	7½	10	Observed Relapse Per cent
Seronegative Primary	18	28	22	50	28	17
Seropositive Primary	49	27	20	51	29	10
Early Secondary	71	25	21	52	27	10
Late Secondary	70	29	19	49	33	6
Total	208	27	20	50	29	9

Table 4.—Important Variables According to Race and Sex

Race and Sex	Number of Patients	Stage of Disease Per cent with Seroneg. Prim.	Seropos. Prim.	Early Sec.	Late Sec.	Abnormal CSF Per cent With	Duration of Treatment (Days) Per cent in 3¾	7½	10	Observed Relapse Per cent
Negro, Male	58	16	29	24	31	26	17	53	29	7
Negro, Female	63	3	8	44	44	22	24	48	28	11
White, Male	37	16	43	22	19	38	19	51	30	11
White, Female	50	2	22	42	34	26	20	50	30	8
Total	208	9	24	34	34	27	20	50	30	9

From Fig. 5 the observation was made that the longer the duration of the disease, the longer the period to serologic negativity following treatment. Before accepting this observation as valid, other factors which might account for the observed difference in serologic behavior deserve consideration: (1) the incidence of asymptomatic neurosyphilis; (2) the efficacy of the treatment schemes employed; and (3) the incidence of subsequent relapse in the respective groups. Data pertaining to these are presented in Table 3. *A priori*, it would be anticipated that the incidence of asymptomatic neurosyphilis would increase proportionately with increasing duration of infection. It is surprising, therefore, that the prevalence of abnormalities in the cerebrospinal fluid is almost identical in the four groups (seronegative primary, 28%; seropositive primary, 27%; early secondary, 25%; late secondary, 29%). In regard to the type of treatment (this is most easily measured in terms of duration*) there are no significant differences between the four stages of disease. Since patients who subsequently relapsed are included in the serologic trends until either clinical relapse† or the initial evidence of a subsequently confirmed serorelapse occurred, it is important to determine the extent to which each group under consideration is weighted with those patients who ultimately relapsed. Relapse subsequently occurred in 10% of patients with seropositive primary syphilis, in 10% with early secondary syphilis, and in 6% with late secondary syphilis. Thus, this factor could not have contributed to

* As judged by ultimate relapse, the least efficacious of these 3 treatment schedules appears to be the shortest in duration (3¾ days). There is as yet no clear-cut difference between the 7½ and 10 day schedules.

† Because of the difficulty of differentiating reinfection from relapse, the reappearance of infectious lesions following treatment has been considered a treatment failure, i.e., relapse.

the observed serologic response.* It would appear, therefore, that duration of infection *per se* accounts for the retardation in rate of fall of serum reagin.

Other factors are apparently of less importance in regard to serologic response. In Fig. 6 it was noted that Negro females seemed to remain seroresistant longer than other race and sex groups. Other related factors are studied in Table 4. It is seen that (1) a higher proportion of Negro females (44%), had *late* secondary syphilis, *i.e.*, longer duration of infection, than any of the other groups, (2) a higher proportion of Negro females (24%) than of any of the other groups received the shortest and presumably the least efficacious treatment schedule, (3) cerebrospinal fluid abnormalities were not related since the Negro female group had the lowest percentage of abnormalities, and (4) subsequent relapse was not an important factor since an equal proportion (11%) of Negro females and white males suffered relapse. Although the longer duration of the disease and the shorter treatment schedule *may* have been concerned in the prolonged serologic response recorded in the Negro female group, it is entirely possible that this is a chance observation based on insufficient data, and that with a larger series of patients this would not hold true.

The effects of age were seen in Fig. 7. These differences may not be significant, yet it is of importance to determine whether factors existing in the basic material (Table 5) can account for the observed variations. The group which showed the slowest response in Fig. 7 (under 20) was composed of 62% Negro females. Seventy-eight per cent were patients with secondary syphilis. The 35 and over age group contained slightly but not significantly more late secondary syphilis than the youngest age group. The age group showing the most prompt response (25–34 years) had the highest proportion of patients with primary syphilis. The presence of abnormalities in the cerebrospinal fluid again did not seem to influence the rate of fall of serum reagin, since the incidence of these abnormalities was highest in the age group showing the most rapid serologic response. Similarly, treatment, measured in terms of duration, seemingly was not concerned in this response. Relapse, in view of its distribution by age groups—under 20, 13%; 20–24, 9%; 25–34, 7%; 35 and over, 4%—may have exerted a retarding influence, since the group with the highest incidence showed the most prolonged response.

From these tables there are no indications that invasion of the central nervous system by *T. pallida* has an appreciable effect on the rate of fall of serum reagin providing treatment has been adequate.

TABLE 5.—IMPORTANT VARIABLES ACCORDING TO AGE

Age Group (years)	Number of Patients	Race and Sex Per cent With				Stage of Disease Per cent With				Abnormal CSF Per cent With	Duration of Treatment (days) Per cent in			Observed Relapse Per cent
		CM	CF	WM	WF	Seroneg. Prim.	Seropos. Prim.	Early Sec.	Late Sec.		3¾	7½	10	
Under 20	53	25	62	2	11	9	13	40	38	15	17	57	26	13
20–24	64	22	31	16	31	9	25	36	30	23	20	48	31	9
25–34	68	34	13	29	24	10	29	29	31	38	26	46	28	7
35 & over	23	35	4	26	35	..	26	30	44	30	9	57	35	4
Total	208	28	30	18	24	9	24	34	34	27	20	50	30	9

* The proportion of relapses in the 3 diagnostic categories does not correspond with Eagle's much larger experience based on the results of semi-intensive arsenical treatment of 4,823 patients with early syphilis.[5] In his material, there was a linear relation between relapse and duration of infection, a higher percentage being observed after secondary than after seropositive primary syphilis. In the present material, a total of only 19 relapses (17 mucocutaneous, 2 serologic alone) have thus far occurred. Several of the primary syphilis group classified as relapse, probably if not certainly, represent instances of reinfection. The difference in the incidence of relapse in early and in late secondary syphilis is not significant.

On the contrary, there is evidence both in the present study and in the material of Crosby and Campbell that the blood serologic response is independent of the presence or absence of abnormalities in the cerebrospinal fluid.

Summary. 1. The serologic response during the first year following penicillin therapy is recorded in 208 patients with previously untreated primary or secondary syphilis. Serologic trends are compared with previously published observations during arsenical therapy. The effects of age, race, sex, duration of infection, and asymptomatic neurosyphilis on serologic response are considered.

2. The serologic response observed during the first 8 weeks following penicillin therapy for early syphilis is comparable to that previously reported during weekly treatment with the several arsenical drugs. Since some of these latter agents are known to be therapeutically inferior, this observation reemphasizes the fact that, in the final evaluation of antisyphilitic drugs, serologic response is not an all-important criterion of therapeutic efficacy.

3. In a comparison of the serologic response during the first 8 weeks following penicillin with that previously recorded during weekly arsenical treatment by stage of disease (seropositive primary, early secondary, and late secondary syphilis), an apparent retardation in the rate of fall of serum reagin following penicillin was observed.

4. The serologic trends recorded during the first year following penicillin therapy provide evidence of a linear relationship between duration of infection and rate of fall of serum reagin—the longer the duration of disease, the slower the serologic response.

5. A study of the serologic response by age, race, and sex demonstrated, in this material, a delayed rate of fall of serum reagin in Negro females and in the youngest age-group (under 20 years). Evidence is presented that the retarded response observed is related (in these groups) to a higher percentage of patients who had (*a*) longer duration of disease, (*b*) the least efficacious treatment scheme, or (*c*) a high incidence of subsequent relapse, or to a combination of these factors.

6. The presence of early asymptomatic neurosyphilis exerted no apparent retarding effect on the rate of fall of serum reagin.

7. The importance of the several factors which influence results in comparative serologic studies is discussed. These include (1) the statistical method of analysis, (2) variations in sensitivity of serologic tests for syphilis, (3) differences in methods of reporting quantitative results and in defining the end-point in quantitative techniques. The lack of correlation in this study between the serologic response following penicillin and that recorded during the first 8 weeks of arsenical therapy when compared (1) by drug and (2) by stage of disease is related to these statistical and technical factors.

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THE ABSORPTION AND ELIMINATION OF SULFADIAZINE ADMINISTERED AS TABLETS, AS A GROUND (MICRONIZED) POWDER AND AS MICROCRYSTALS*

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That sulfonamides given by mouth are absorbed to the same extent no matter in what pharmaceutical form they may be administered, is the commonly accepted opinion. Evidence to the contrary has been presented in a few papers, notably that of Reinhold, Phillips and Flippin.[3] The report of the work of these authors was published in the August 1945 issue of this Journal, shortly after the experiments to be described below were begun. Reinhold *et al.* have reviewed the pertinent literature, from which they drew the conclusion that it had been shown that "in microcrystalline form the activity (of sulfonamides) is enhanced, but the information available is limited." Describing their own experience with patients from the medical wards of the Philadelphia General Hospital, Reinhold, Phillips and Flippin found that microcrystalline sulfadiazine was absorbed into the blood stream and excreted in the urine more rapidly during the first 6 hours after administration than was sulfadiazine given in tablet form. The experiments to be described herein were performed upon healthy, human volunteers. The results confirm those of Reinhold *et al.* in showing that the smaller the particle size of administered sulfadiazine, the faster the absorption and elimination; at the same time, a considerable body of new data is presented upon the metabolism of these different sized particles of administered sulfadiazine.

Technique. The 3 pharmaceutical forms of sulfadiazine investigated were as follows: The first consisted of tablets of sulfadiazine purchased on the open market. The second preparation was composed of micronized sulfadiazine suspended in an aqueous vehicle, containing volatile oils, flavoring and coloring agents. This material was prepared by the Pitman-Moore Company of Indianapolis and consisted of sulfadiazine which had been reduced to small spheres, somewhat larger in size than the microcrystals, by a process of grinding. The actual composition of the suspension was described to us as follows: sulfadiazine 10.12 gm., oil of orange 0.002 ml., amaranth 0.0038 gm., sitro or lemon yellow 0.0094 gm., citric acid 0.128 gm., benzoic acid 0.25 gm., kelgin q.s., sucrose 23.97 gm. and distilled water to 100 ml. Reinhold *et al.* found that sugar and flavoring agents had no appreciable effect of themselves upon the absorption and elimination of sulfadiazine, so that the effect or lack of effect of the vehicle and suspending medium was not investigated in the present work. The third preparation consisted of microcrystalline (semi-colloidal) sulfadiazine suspended in the same medium as the micronized material, the size of the microcrystals being of the same order as those employed by Reinhold *et al.* in their suspension. Both of these latter preparations were provided us by the Pitman-Moore Company and we are also indebted to the same Company for a grant-in-aid of this research.

Each preparation was given to a total of 30 healthy, human volunteers, in a dose containing 4 gm. of the drug, at 10 A.M. on the morning of an experiment. At the same time, the volunteers drank 1 pint of water. At intervals of 0.5, 1, 2, 4 and 6 hours after administration of the drug, a

* This paper was presented in preliminary form at the annual meeting of the American Society for Pharmacology and Experimental Therapeutics, Atlantic City, March 1946.

sample of oxalated blood was obtained as well as the volume of urine which had accumulated during the several intervals. Total and free (and by difference, combined) sulfadiazine were estimated upon an aliquot of whole blood and upon an aliquot of the oxalated plasma, at each interval. The volume of urine was noted and total, free and combined sulfadiazine determined upon each sample before and after centrifuging. The method used for estimating sulfadiazine was a slight modification of the technique of Bratton and Marshall.[1] Upon each sample of urine, a test for albumin was made and the pH determined with the aid of a Coleman pH electrometer. The centrifuged specimen of urine was examined microscopically for crystals of acetylated sulfadiazine, red blood cells, white blood cells and casts. In addition, a close record was kept of the clinical condition of the volunteer with the especial object of detecting any signs of untoward reactions or toxic effects.

The experiments were rotated so that at any one time, approximately equal numbers of volunteers had been allocated to each of the 3 preparations. The results were tabulated and the means, standard deviations and errors of the means and Pearson's coefficients of variation calculated after the formulæ of Hill.[2]

and gave higher blood levels of sulfadiazine than did the tablets. Also, the suspension of microcrystals was absorbed more rapidly and produced higher concentrations of the drug in blood than did the suspension of micronized powder or the tablets. In almost all instances, the standard error of the mean difference between blood values at any given interval after administration of the 3 preparations was many times the mean difference, thus making the possibility of the mean difference occurring by chance extremely unlikely. Thus, for example, the standard error of the mean difference at 0.5 hours in the concentration of total sulfadiazine in whole blood after giving tablets *versus* after the micronized powder was about 4 times the mean difference, making the chances approximately 1 in 1000 that the difference could have been due purely to chance. Comparing corresponding values after giving the tablets *versus* the microcrystals at the same interval, the standard error of the mean difference was some 10 times the mean difference. In the instance of the remaining possible comparison of corresponding values at the

TABLE 1.—THE CONCENTRATION OF SULFADIAZINE IN MG. PER 100 ML. OF WHOLE BLOOD FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Concentration in whole blood: mean ± standard error				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
			Total Sulfadiazine		
Tablets	0.45±0.06	1.3±0.17	2.8±0.21	5.6±0.41	5.9±0.46
Micronized powder	0.85±0.10	1.8±0.20	3.7±0.26	6.5±0.34	6.5±0.35
Microcrystals	1.30±0.09	2.7±0.14	4.5±0.22	7.1±0.41	7.1±0.41
			Free Sulfadiazine		
Tablets	0.43±0.06	1.2±0.16	3.0±0.24	5.4±0.36	5.7±0.45
Micronized powder	0.87±0.10	1.6±0.17	3.6±0.21	6.2±0.28	6.1±0.30
Microcrystals	1.30±0.08	2.6±0.14	4.3±0.16	6.9±0.32	6.4±0.53
			Combined Sulfadiazine		
Tablets	0.02	0.1	−0.2	0.2	0.2
Micronized powder	−0.02	0.2	0.1	0.3	0.4
Microcrystals	0.0	0.1	0.2	0.2	0.7

WHOLE BLOOD SULFADIAZINE. Values for total, free and combined sulfadiazine in whole blood have been summarized in Table 1. From the values obtained, it is obvious that the suspension of micronized sulfadiazine was absorbed more rapidly

same interval, that is after micronized powder *versus* after microcrystals, the comparable statistical figure is about 7. Similar calculations were made for the remaining figures given in Table 1, and the probability of the mean difference

being due purely to chance drops to about 1 in 20 only in the instances of whole blood total and free sulfadiazine at 4 and 6 hours.

Values for whole blood combined sulfadiazine were low and variable as would be expected, since it is well known that patients upon sulfadiazine therapy have little combined sulfadiazine in blood and since the value for this fraction is obtained by difference between free and total sulfadiazine, it accumulates the errors involved in both these estimations, thus making the standard deviation of combined sulfadiazine means extremely variable. Hence only the mean values for combined sulfadiazine have been reported in Table 1, since in some instances the mean was actually negative and also the standard error was often greater than the mean. The only significant conclusion which may be drawn from these figures is that values for combined sulfadiazine are low; while there were mean differences following administration of the different preparations of the drug, no statistical significance could be proven for the differences. It is possible that the smaller sized particles of sulfadiazine produce a higher concentration of the combined drug in blood, but many more volunteers per group would be required to prove this statistically.

In general, Pearson's coefficient of variation was high for the initial readings at 0.5 and 1 hour but fell to a mean value of about 25 in most instances at 4 and 6 hours in both whole blood (Table 1) and blood plasma (Table 2). This indicated that while early values for blood sulfadiazine concentration were rather variable, the concentration in each group became more nearly alike after 4 hours. Similar results were obtained with values for sulfadiazine in urine, so that no further reference need be made to Pearson's coefficient of variation.

The *conclusions* to be derived from these results are that sulfadiazine is most rapidly absorbed when administered by mouth in the form of a suspension of microcrystals, somewhat less rapidly absorbed when given as a suspension of micronized powder and least rapidly absorbed when taken as tablets. After about 6 hours from the time of administration, the concentration of total and free sulfadiazine in whole blood is approximately the same, for all practical purposes, no matter in which pharmaceutical form it has been given. The concentration of combined sulfadiazine in whole blood does not reach appreciable values until 6 hours after administration, when it averages 5 to 10% of the total whole blood sulfadiazine, and while the mean values are higher the smaller the particle size of the administered sulfadiazine, it was not possible to prove a statistically significant difference with the number of samples available.

Plasma Sulfadiazine. Corresponding values for total, free and combined sulfadiazine in plasma have been summarized in Table 2. From these results, the same general conclusions may be drawn as were in the instance of whole blood, *i. e.*, that microcrystalline sulfadiazine was absorbed most rapidly, the micronized powder next and the tablets least rapidly, with all concentrations of sulfadiazine in blood plasma tending to approximate each other by the end of 6 hours after administration no matter in which form administered. Almost all concentrations of sulfadiazine in blood plasma were higher than those in whole blood, indicating that during the first 6 hours of the experiment at least, there is more sulfadiazine in plasma than in the red blood cells. There were some differences in the distribution of sulfadiazine between plasma and red blood cells following administration of the 3 pharmaceutical forms of the drug. By comparing the mean of all mean values at the 5 intervals studied, the level of plasma total sulfadiazine was 116% of that of whole blood sulfadiazine following administration of tablets, 143% following administration of the suspension of micronized powder and 129% following administration of the microcrystals. Corresponding values for plasma-free sulfadiazine were 116, 138 and 133% respectively and again

the values for plasma combined sulfadiazine were so variable as to make a comparison of little significant value. While mathematically there was little difference in the distribution of sulfadiazine between blood plasma and the red blood cells following administration of the 3 pharmaceutical forms of the drug, the mean percentage distributions suggest that the drug may be present in plasma in relatively greater concentrations than in the red blood cells following the taking of the smaller sized particles of sulfadiazine.

bled in Table 3. In this table, the results are expressed in mg. of the respective forms of the drug per 100 ml. of urine, and while the volume of urine per stated interval varied a good deal from person to person, the average volume per interval was about the same with each preparation of the drug.

It is apparent that the concentration of total, free and combined sulfadiazine was greater following administration of those preparations which were absorbed the more rapidly into the blood stream.

TABLE 2.—THE CONCENTRATION OF SULFADIAZINE IN MG. PER 100 ML. OF BLOOD PLASMA FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Concentration in blood plasma: mean ± standard error				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
			Total Sulfadiazine		
Tablets	0.22±0.04	0.93±0.13	3.1±0.23	6.5±0.64	7.1±0.80
Micronized powder	1.20±0.19	2.50±0.35	4.8±0.41	9.5±0.49	9.8±0.59
Microcrystals	1.70±0.19	3.20±0.34	5.6±0.40	9.5±0.65	8.9±0.59
			Free Sulfadiazine		
Tablets	0.28±0.04	0.92±0.14	3.5±0.41	6.4±0.59	7.5±0.85
Micronized powder	1.00±0.17	2.10±0.41	4.6±0.49	8.8±0.47	8.9±0.59
Microcrystals	1.80±0.18	3.40±0.29	5.8±0.33	9.1±0.52	8.5±0.50
			Combined Sulfadiazine		
Tablets	−0.06	0.1	−0.4	0.1	−0.4
Micronized powder	0.2	0.4	0.2	0.7	0.9
Microcrystals	−0.1	−0.2	−0.2	0.4	0.4

Assuming this to be so, it may be *concluded* that the oral administration of sulfadiazine in the form of a suspension of microcrystals or micronized powder is followed by more rapid absorption of the drug from the gastro-intestinal tract, higher concentrations in blood plasma, less diffusion into the red blood cells and, as will be shown, more rapid elimination in urine, than the oral administration of sulfadiazine as tablets, at least for the first 6 hours after taking the drug.

CONCENTRATION OF SULFADIAZINE IN URINE. The concentration of total, free and combined sulfadiazine was estimated in uncentrifuged and well-shaken aliquots of urine which had been collected by emptying the bladder at the same intervals that blood was withdrawn, no uncollected urine being voided between these intervals. The mean concentrations and their standard errors have been assembled in Table 3. In this table, the results are expressed in mg. of the respective forms of the drug per 100 ml. of urine, and while the volume of urine per stated interval varied a good deal from person to person, the average volume per interval was about the same with each preparation of the drug.

It is apparent that the concentration of total, free and combined sulfadiazine was greater following administration of those preparations which were absorbed the more rapidly into the blood stream. This was so until about the 4th hour after which the differences were less marked and consistent. Up to the 4th hour, mean differences in concentration at each interval between those taking the 3 preparations of the drug were of the order of 2.5 to 4 times the standard error of the mean difference.

CONCENTRATION OF SULFADIAZINE IN CENTRIFUGED URINE. It is well known that sulfadiazine, especially in the combined form, is relatively insoluble in urine. Since the 2 suspensions of sulfadiazine produced higher concentrations of all forms of the drug in urine than did the tablets, there was the possibility that the suspensions might produce a sulfadiazine crystalluria. To investigate this, each sample of urine was centrifuged and an aliquot of the supernatant urine analyzed as before. The mean values obtained in the 3 groups, together with the standard

errors of the means, have been assembled in Table 4. By comparing the results given in Tables 3 and 4, it is obvious that there were no marked differences in the concentration of total, free or combined sulfadiazine in centrifuged *versus* uncentrifuged urine. The conclusion may be drawn that providing a sufficient volume of water is taken with the drug, there is no danger of sulfadiazine crystalluria from the 2 suspensions, even though the concentration of the drug in urine is a good deal higher than following use of the tablets. In view of the results obtained, however, it would be well to make certain that a large volume of water or other fluids be taken if one or other of the suspensions of sulfadiazine be used in therapy.

TOTAL URINARY OUTPUT OF SULFADIAZINE. To estimate the total mg. output of total, free and combined sulfadiazine at the various intervals collected, the concentration of the drug per ml. was multiplied by the number of ml. of urine collected and the means and standard errors have been assembled in Table 5. The results indicate that those pharmaceutical preparations which were absorbed the more quickly into the blood stream, were also excreted in greater amount in urine, even up to 4 and 6 hours after administration. With a few exceptions, the difference between the mean total mg. outputs of the 3 pharmaceutical forms of sulfadiazine was of the order of 2.5 to 4 times

TABLE 3.—THE CONCENTRATION OF SULFADIAZINE IN MG. PER 100 ML. OF UNCENTRIFUGED URINE FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Concentration in urine: mean ± standard error				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
Total Sulfadiazine					
Tablets	1.7±0.21	8.4±1.4	31.4±4.0	112± 9.2	182±16.5
Micronized powder	5.9±0.83	21.4±4.3	47.0±7.4	121±13.8	214±21.7
Microcrystals	8.7±1.40	30.1±4.9	69.2±9.5	135±11.2	176±13.6
Free Sulfadiazine					
Tablets	1.8±0.20	7.8±1.3	28.0±3.5	99.5± 8.3	141±13.0
Micronized powder	5.8±0.84	18.8±3.2	39.4±5.8	97.5±13.0	167±14.7
Microcrystals	8.0±1.30	25.7±4.2	61.4±5.3	113±10.9	155± 6.5
Combined Sulfadiazine					
Tablets	−0.1±0.07	0.6±0.26	3.4±0.95	12.5± 2.3	41± 4.8
Micronized powder	0.1±0.24	2.6±0.86	7.6±2.00	23.5± 3.0	47± 4.0
Microcrystals	0.7±0.16	4.4±0.87	7.8±2.20	22.0± 2.7	21± 3.2

TABLE 4.—THE CONCENTRATION OF SULFADIAZINE IN MG. PER 100 ML. OF CENTRIFUGED URINE FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Concentration in centrifuge urine: mean ± standard error				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
Total Sulfadiazine					
Tablets	1.9±0.35	7.3±2.0	31.6± 5.9	110±12.7	178±21.2
Micronized powder	6.9±1.50	23.8±5.4	47.6± 9.4	123±17.9	206±23.0
Microcrystals	9.9±2.00	24.2±5.8	69.7±17.9	140±18.0	192±17.8
Free Sulfadiazine					
Tablets	1.8±0.26	7.0±1.9	28.8± 5.6	94±11.6	145±18.5
Micronized powder	7.3±1.40	21.4±5.0	48.5± 8.0	107±18.4	170±20.1
Microcrystals	9.3±1.80	21.6±4.9	59.5±13.9	120±17.8	163±14.6
Combined Sulfadiazine					
Tablets	0.1±0.10	0.3±0.17	2.8± 0.56	16± 2.3	33± 4.3
Micronized powder	−0.4±0.21	2.4±0.82	0.9± 2.80	16± 2.1	36± 5.4
Microcrystals	0.6±0.60	2.6±0.88	10.2± 1.90	20± 2.5	29± 5.7

TABLE 5.—THE TOTAL MG. OUTPUT OF SULFADIAZINE IN URINE FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Mg. output of sulfadiazine: mean ± standard error				
	0 to 0.5 hr.	0.5 to 1 hr.	1 to 2 hrs.	2 to 4 hrs.	4 to 6 hrs.
			Total Sulfadiazine		
Tablets	1.79 ± 0.30	6.19 ± 0.97	25.4 ± 2.5	128 ± 13.0	190 ± 32.3
Micronized powder	4.40 ± 0.51	10.70 ± 2.00	37.2 ± 3.7	141 ± 15.1	228 ± 24.1
Microcrystals	6.40 ± 0.52	18.90 ± 3.00	57.5 ± 7.0	200 ± 20.2	216 ± 18.8
			Free Sulfadiazine		
Tablets	1.96 ± 0.29	6.02 ± 0.91	23.2 ± 1.2	115 ± 12.4	153 ± 17.3
Micronized powder	4.10 ± 0.48	9.50 ± 1.50	32.4 ± 3.1	125 ± 11.9	186 ± 19.1
Microcrystals	5.40 ± 0.63	16.40 ± 2.30	46.0 ± 5.3	170 ± 17.6	162 ± 19.8
			Combined Sulfadiazine		
Tablets	0.17	0.17	2.2	13	37
Micronized powder	0.3	1.2	4.8	16	42
Microcrystals	1.0	2.5	11.5	30	54

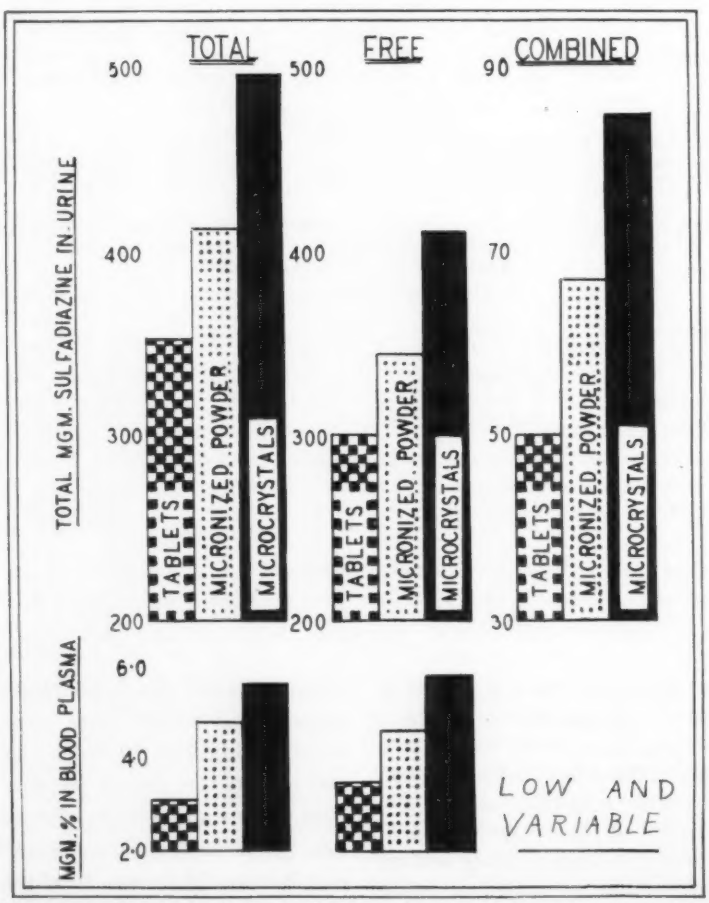

FIG. 1.—The 6 hour output of sulfadiazine in urine after administration of the drug in the form of tablets, a micronized powder suspension and as a suspension of microcrystals, compared with a representative example of the concentration in blood plasma.

the standard error of the mean difference at each interval.

The total mg. output in urine of total, free and combined sulfadiazine was calculated for the 6 hour period and for each pharmaceutical form in which the drug had been given. The results were averaged and these averages have been shown as a block diagram in Figure 1. To avoid a chart of confusing appearance, the standard errors of the means have not been indicated in Figure 1, but in the case of each form of the drug in urine, there was a significant difference between the 3 pharmaceutical forms of the drug. In order to show that the accumulated urinary output of sulfadiazine varied with the concentration in blood, except in the case of combined sulfadiazine, the concentration of the drug in blood plasma at the middle (2nd hour) interval was selected as representative of the blood levels and included in Figure 1. The data charted in Figure 1 summarize in a visual manner the main relationships found between blood and urine values and illustrate the quantitative differences in metabolism of the 3 types of sulfadiazine used in this study.

Table 6.—The Effect of Oral Administration of 4 Gm. of Sulfadiazine in Various Pharmaceutical Forms Upon the pH of Urine

Pharmaceutical form	Mean pH of urine				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
Tablets	5.9	5.9	5.8	5.7	5.8
Micronized powder	5.5	5.8	5.6	5.6	5.7
Microcrystals	5.4	5.7	5.5	5.5	5.5

General Examination of the Urine. Since damage to the kidneys is a fairly common reaction to sulfadiazine therapy, a general examination was made upon each sample of urine. The pH of urine was determined with the aid of a Coleman pH electrometer and the mean values have been assembled in Table 6. The pH of urine was not markedly affected by administration of these drugs. Most values were slightly on the acid side of normal. The most acid pH values were found following the use of the suspension of microcrystals which again suggests that when this preparation is used, there should be given plenty of fluids with or without alkali therapy as well.

The sediment of centrifuged specimens of urine was examined for crystals of free and combined sulfadiazine. In only a few instances were crystals found present, which was probably due to the fact that a considerable volume of water had been taken with the drug. Similarly there were little or no albuminuria, red blood cells, white blood cells nor casts found present in the urine.

Reactions to Sulfadiazine. During the course of this and of a following investigation, in which lactates were added to the suspension of microcrystals, sulfadiazine was given a total of between 150 and 200 times. A majority of the volunteers had had sulfadiazine therapy at least once before for some infection. It was expected, therefore, that there might have been some sensitization to the drug as occurs for example with sulfathiazole and a detailed clinical record was kept of each volunteer during and for a period up to almost a year in some cases after the experiment. In 1 volunteer, there was a slight urticarial rash the day after taking the drug but this rash did not appear again when the same person was given a second dose of sulfadiazine some 2 to 3 weeks later. Apart from this questionable reaction, there were no toxic effects noted in any of the volunteers.

Summary. Sulfadiazine was administered orally in 3 forms, (*a*) as tablets, (*b*) as a suspension of crushed or micronized powder and (*c*) as a suspension of microcrystals, in a dose of 4 gm. of the drug with 1 pint of water, to a total of 90 human volunteers, 30 given each preparation, with the following results: 1. As indicated

by estimation of whole blood and blood plasma sulfadiazine at intervals from 0.5 to 6 hours after administration, the drug was found most rapidly absorbed from the gut when given as microcrystals, next most rapidly as the micronized powder and least rapidly as the tablets.

2. Six hours after administration, the concentration of sulfadiazine in blood was almost the same no matter in which form it had been given.

3. The concentration of combined sulfadiazine in blood did not reach appreciable values until about 6 hours after administration, at which time the concentration was higher following the use of the micronized powder and microcrystals.

4. There was some indication that when sulfadiazine is given as the micronized powder or as microcrystals, it passes from plasma into the red blood cells to a relatively less extent than when given as tablets.

5. The concentration of total, free and combined sulfadiazine in both centrifuged and uncentrifuged samples of urine collected at the same intervals as blood was withdrawn, was greatest following administration of the microcrystals, next following the micronized powder and least following the tablets. Values for the total output of sulfadiazine in urine roughly paralleled the blood values.

6. Little or no evidence was found of sulfadiazine crystalluria or of renal damage.

7. The urinary pH was on the acid side of normal, the most acid urine being obtained after use of the microcrystals.

8. Although many and probably most of the volunteers had had previous sulfadiazine therapy, there were no untoward or toxic reactions to the drug.

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THE EFFECT OF SODIUM AND POTASSIUM LACTATES UPON THE ABSORPTION AND ELIMINATION OF MICROCRYSTALLINE SULFADIAZINE*

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In a previous communication,[1] it was shown that administration of a suspension of microcrystalline sulfadiazine possessed certain advantages over the use of tablets in that higher concentrations of the drug were obtained in blood and attained more quickly. At the same time, use of the suspension of microcrystals was followed by higher concentrations of the drug in urine, thus increasing the danger of sulfadiazine crystalluria and renal damage. To avoid these latter effects, a large fluid intake, preferably with alkali therapy as well, is indicated when these suspensions are employed therapeutically.

Sodium bicarbonate is the drug commonly employed to render the urine more alkaline during systemic sulfonamide therapy. However, there are several disadvantages in the use of sodium bicarbonate, especially if it is to be added to an aqueous preparation of sulfonamides, such as the suspension of microcrystalline sulfadiazine, and kept for some time before use. To affect appreciably the pH of urine, several grams of sodium bicarbonate must be taken by mouth. If dissolved in an aqueous preparation, such as the suspension of microcrystalline sulfadiazine referred to above, it slowly decomposes into the much more strongly alkaline sodium carbonate, with liberation of carbon dioxide, even at room temperature. The presence of alkaline sodium bicarbonates and carbonates would in time cause decomposition of various ingredients of the suspension of microcrystalline sulfadiazine previously employed.[1] Sodium bicarbonate is soluble in water only to 10% or less, thus requiring a large volume dose of any sodium bicarbonate-sulfadiazine aqueous preparation. If an aqueous, pharmaceutical preparation of sulfadiazine happened to be, or to become, acid in reaction, carbon dioxide would be set free from any added sodium bicarbonate. These incompatibilities would render unstable and useless any combination of sodium bicarbonate and sulfadiazine in an aqueous pharmaceutical preparation meant to be kept for any length of time.

On the other hand, sodium lactate is readily soluble in water, forming a solution which is stable, about neutral in reaction and, when taken by mouth, it is converted into sodium bicarbonate in the body, so that the net pharmacologic effect is similar, after absorption, to that of giving sodium bicarbonate. We have therefore studied the effect on absorption and elimination in the body, of a suspension of microcrystalline sulfadiazine, similar in composition to that previously described, to which had been added 8.5 gm. of sodium lactate per 100 ml. of the suspension. The resulting preparation had a pleasant taste, the most pleasant of all of the suspensions of microcrystalline sulfadiazine studied in this and the previously reported investigation.[1]

Ohnysty and Wolfson[4] tried potassium bicarbonate in place of sodium bicarbonate, on the grounds that potassium bicarbonate is diuretic and does not promote

* This paper was presented in preliminary form at the annual meeting of the American Society for Pharmacology and Experimental Therapeutics, Atlantic City, March 1946.

retention of water in the extracellular body fluids as does sodium bicarbonate. They found potassium bicarbonate effective in preventing sulfonamide crystalluria. Therefore it was decided to compare sodium and potassium lactates and a further suspension of microcrystalline sulfadiazine, similar in composition to that previously described[1] but with the addition of 8.5 gm. of potassium lactate per 100 ml. of suspension, was investigated. The latter preparation was somewhat bitter and much less pleasant to the taste than was the preparation made with sodium lactate. These 2 preparations of lactates, together with the simple suspension of microcrystalline sulfadiazine, were made and placed at our disposal by the Pitman-Moore Company of Indianapolis, which company also provided us with a grant-in-aid of this research.

Technique. The suspensions of microcrystalline sulfadiazine with sodium and with potassium lactates were each given to 30 healthy, human volunteers, in a dose equivalent to 4 gm. of sulfadiazine, and the results compared with those previously reported for the microcrystalline suspension without the lactates.[1] Each volunteer voided his or her urine at 10 A.M. the day of the experiment and then took the respective suspension of the drug, together with a pint of water. At intervals of 0.5, 1, 2, 4 and 6 hours after administration, a sample of oxalated blood was obtained and the accumulated volume of urine collected, no urine having been voided and discarded between intervals. Determinations as described below and identical to those previously reported[1] were made, sulfadiazine being estimated by a slight modification of the method of Bratton and Marshall.[2] The results were statistically analyzed as in the previous communication,[1] using the formulæ of Hill.[3]

BLOOD SULFADIAZINE. Means and their standard errors for the concentration of total, free and combined sulfadiazine in oxalated whole blood have been assembled in Table 1. The addition of lactates significantly accelerated the rate of absorption of sulfadiazine from the suspension of the microcrystals. In this respect, sodium lactate was more effective than potassium lactate. The effect lasted until about the 4th hour after administration, after which there were no significant differences in the concentration of total and free sulfadiazine in whole blood. The concentration of combined sulfadiazine was low and variable and the values of so little significance that only means have been given in Table 1.

Differences in the concentration of sulfadiazine in blood plasma (Table 2) were of the same nature as those in whole blood, the lactates accelerating the absorption of microcrystalline sulfadiazine during the first 4 hours after administration. During the first 2 hours after administration, the average levels of total and free sulfadiazine in blood plasma were about 1.3 times those in whole blood, indicating a higher concentration in plasma than in the red blood cells. For all practical purposes, there were no differences in the distribution of sulfadiazine between plasma and red blood cells following the giving of the 3 pharmaceutical forms of the drug.

The differences in the rate of absorption of the 3 preparations of sulfadiazine were not due to differences in the pH of the suspensions. As measured in a Coleman pH electrometer and checked by color indicators, the pH of the suspension of microcrystals alone was 3.6, of the microcrystals plus potassium lactate 3.5 and of the microcrystals plus sodium lactate 5.0. From the evidence available, it was not possible to explain why lactates accelerate the rate of absorption of microcrystalline sulfadiazine. In conclusion, of the 5 pharmaceutical preparations of sulfadiazine studied in this and the previously reported investigation,[1] the preparation of microcrystals with sodium lactate proved to be the most efficacious in that it was pleasant to taste, most quickly absorbed from the gastro-intestinal tract, gave higher concentrations in whole blood and in blood plasma and, as will be described, was most quickly excreted in urine and made the urine least acid. These results, therefore, indicate that in sulfadiazine therapy, the

suspension of microcrystalline sulfadiazine with sodium lactate, as herein used, is the pharmaceutical preparation of choice, especially in the therapy of infants and in other instances where tablets are contraindicated for one reason or another.

URINARY SULFADIAZINE. The concentrations of sulfadiazine in urine have been

TABLE 1.—THE CONCENTRATION OF SULFADIAZINE IN MG. PER 100 ML. OF WHOLE BLOOD FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Concentration in whole blood: mean ± standard error				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
Total Sulfadiazine					
Microcrystals	1.3±0.09	2.7±0.14	4.5±0.22	7.1±0.41	7.1±0.41
" plus K lactate	1.7±0.13	2.9±0.27	4.8±0.22	6.8±0.26	6.4±0.28
" plus Na lactate	2.0±0.19	3.6±0.23	5.4±0.30	7.4±0.39	6.7±0.35
Free Sulfadiazine					
Microcrystals	1.3±0.08	2.6±0.14	4.3±0.16	6.9±0.32	6.4±0.53
" plus K lactate	1.8±0.13	3.1±0.19	4.8±0.22	6.8±0.25	6.1±0.24
" plus Na lactate	2.3±0.18	3.7±0.19	5.6±0.26	7.0±0.35	6.4±0.33
Combining Sulfadiazine					
Microcrystals	0.0	0.1	0.2	0.2	0.7
" plus K lactate	−0.1	−0.2	0.0	0.0	0.3
" plus Na lactate	−0.3	−0.1	−0.2	0.4	0.3

TABLE 2.—THE CONCENTRATION OF SULFADIAZINE IN MG. PER 100 ML. OF BLOOD PLASMA FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Concentration in blood plasma: mean ± standard error				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
Total Sulfadiazine					
Microcrystals	1.7±0.19	3.2±0.34	5.6±0.40	9.5±0.65	8.9±0.50
" plus K lactate	2.0±0.21	4.1±0.40	6.2±0.42	9.0±0.50	8.5±0.39
" plus Na lactate	2.7±0.36	5.2±0.34	7.7±0.51	10.3±0.47	9.1±0.56
Free Sulfadiazine					
Microcrystals	1.8±0.18	3.4±0.29	5.8±0.33	9.1±0.52	8.5±0.50
" plus K lactate	2.0±0.21	4.2±0.32	6.4±0.43	9.1±0.44	8.3±0.39
" plus Na lactate	2.9±0.29	4.9±0.31	7.5±0.42	9.9±0.58	8.4±0.49
Combined Sulfadiazine					
Microcrystals	−0.1	−0.2	−0.2	0.4	0.4
" K lactate	0.0	−0.1	−0.2	−0.1	0.2
" Na lactate	−0.2	0.3	0.2	0.4	0.7

TABLE 3.—THE CONCENTRATION OF SULFADIAZINE IN MG. PER 100 ML. OF UNCENTRIFUGED URINE FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Concentration in urine: mean ± standard error				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
Total Sulfadiazine					
Microcrystals	8.7±1.4	30.1±4.9	69.2±9.5	135±11.2	176±13.6
" plus K lactate	8.0±1.2	35.9±5.4	67.4±9.1	140±12.1	244±22.0
" plus Na lactate	9.7±4.5	48.8±13.8	105.0±10.2	190±18.0	232±20.5
Free Sulfadiazine					
Microcrystals	8.0±1.3	25.7±4.2	61.4±5.3	113±10.9	155±6.5
" plus K lactate	7.5±1.1	32.9±5.1	62.0±8.4	125±11.4	206±24.1
" plus Na lactate	8.9±1.2	42.4±5.3	95.5±9.0	164±15.8	217±18.5
Combined Sulfadiazine					
Microcrystals	0.7±0.16	4.4±0.87	7.8±2.2	22±2.7	21±3.2
" plus K lactate	0.5±0.14	7.0±0.52	5.4±1.0	15±2.6	38±3.4
" plus Na lactate	0.8±0.16	6.4±0.54	9.5±1.6	26±4.3	15±3.9

summarized in Table 3. While in general the mean levels of total and free sulfadiazine were higher when lactates were added to the administered microcrystals, the differences were not statistically significant until after about the 2nd hour, when the concentrations became a good deal higher after use of the preparations containing the lactates. The concentration of combined sulfadiazine varied considerably and it was not possible to state that lactates significantly affected the results.

values are given in Table 4. There was not much difference in the levels of total, free and combined sulfadiazine in centrifuged *versus* uncentrifuged urine, probably due to the large volume of water taken with the drugs and, as will be shown, to the relatively higher values for urinary pH when lactates were added to the microcrystalline suspension.

The total output of total and free sulfadiazine was, in most instances, appreciably and significantly higher following those

TABLE 4.—THE CONCENTRATION OF SULFADIAZINE IN MG. PER 100 ML. OF CENTRIFUGED URINE FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Concentration in centrifuged urine: mean ± standard error				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
	Total Sulfadiazine				
Microcrystals	9.9±2.0	24.2±5.8	69.7±17.9	140±18.0	192±17.8
" plus K lactate	10.0±1.2	35.2±7.9	75.5±12.4	142±19.0	238±23.4
" plus Na lactate	9.4±1.9	37.5±8.5	97.4±11.0	207±33.7	290±35.6
	Free Sulfadiazine				
Microcrystals	9.3±1.8	21.6±4.9	59.5±13.9	120±17.8	163±14.6
" plus K lactate	9.8±2.1	30.8±6.9	66.1±12.9	123±17.7	201±24.1
" plus Na lactate	9.4±1.5	36.7±7.2	86.2±10.6	187±26.5	246±34.8
	Combined Sulfadiazine				
Microcrystals	0.6±0.60	2.6±0.88	10.2± 1.9	20± 2.5	29± 5.7
" plus K lactate	0.2±0.19	4.4±1.4	9.4± 1.6	19± 4.5	47± 5.3
" plus Na lactate	0.0±0.28	0.8±0.62	11.2± 1.6	20± 9.0	44± 7.0

TABLE 5.—THE TOTAL MG. OUTPUT OF SULFADIAZINE IN URINE FOLLOWING ORAL ADMINISTRATION OF 4 GM. OF THE DRUG IN VARIOUS PHARMACEUTICAL FORMS

Pharmaceutical form	Mg. output of sulfadiazine in urine: mean ± standard error					
	0-0.5 hr.	0.5-1 hr.	1-2 hrs.	2-4 hrs.	4-6 hrs.	0-6 hrs.
			Total Sulfadiazine			
Microcrystals	6.4±0.52	18.9±3.0	57.5±7.0	200±20.2	216±18.8	496±43.3
" plus K lactate	7.3±1.5	23.7±2.7	70.9±6.9	224±16.5	263±18.2	580±35.8
" plus Na lactate	8.5±1.0	26.2±3.3	70.5±5.2	228±15.1	254±20.2	576±36.6
			Free Sulfadiazine			
Microcrystals	5.4±0.63	16.4±2.3	46.0±5.3	170±17.6	162±19.8	411±47.6
" plus K lactate	6.8±1.0	21.8±2.6	66.2±6.3	199±14.8	225±18.8	506±36.0
" plus Na lactate	7.9±1.0	25.3±2.7	63.8±4.5	206±15.3	229±17.2	520±36.1
			Combined Sulfadiazine			
Microcrystals	1.0	2.5	11.5	30	54	85
" plus K lactate	0.5	1.9	4.7	25	38	74
" plus Na lactate	0.6	0.9	6.7	22	25	56

In view of the relatively high concentrations of sulfadiazine in urine, there was the possibility of a sulfadiazine crystalluria and hence estimations were made of the concentrations of the several forms of the sulfonamide upon the supernatant urine of centrifuged specimens. These

suspensions of microcrystals containing lactates (Table 5). On the other hand, there were no significant differences in the total output of combined sulfadiazine. In the last column to the right of Table 5, has been given a summation figure for the output of sulfadiazine in urine over the

period of 6 hours of the experiment, and, from the values given in this column, the same general conclusion may be drawn as was with the total outputs at the shorter intervals.

General Examination of Urine and Toxic Reactions. The addition of lactates to the suspension of microcrystalline sulfadiazine made the urine definitely less acid, as may be seen from the mean values for urinary pH assembled in Table 6. Of the 2 lactates, sodium lactate was the more effective in making the urine less acid. In all of these volunteers, only 1 or 2 instances of transient albuminuria were seen, and the sediment from the centrifuged specimens of urine showed little evidence of sulfadiazine crystalluria. There was little or no evidence of renal damage as indicated by the absence or near absence of red blood cells, white blood cells and casts in the urinary sediment. There were no untoward or toxic clinical reactions.

TABLE 6.—THE EFFECT OF ORAL ADMINISTRATION OF 4 GM. OF SULFADIAZINE IN VARIOUS PHARMACEUTICAL FORMS UPON THE PH OF URINE

Pharmaceutical form	Mean pH of urine				
	0.5 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
Microcrystals	5.4	5.7	5.5	5.5	5.5
" plus K lactate	5.5	5.7	6.0	6.0	6.1
" plus Na lactate	5.5	6.1	6.2	6.3	6.3

Summary. 1. Sodium and potassium lactates were separately added to a suspension of microcrystalline sulfadiazine and each preparation was given orally in a dose of 4 gm. of sulfadiazine to 30 human volunteers.

2. The lactates accelerated the absorption of sulfadiazine microcrystals from the gastro-intestinal tract and gave higher initial concentrations of the drug in whole blood and in blood plasma.

3. Lactates also accelerated the output of total and free sulfadiazine in urine and increased the urinary pH. There was no evidence of renal damage nor of other untoward clinical reactions.

4. In all these respects, the preparation of microcrystals with sodium lactate was more effective than the preparation made with potassium lactate and in addition the preparation made with sodium lactate had a much more pleasant taste.

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HYPOTHERMIA AND ELEVATED SERUM MAGNESIUM IN A PATIENT WITH FACIAL HEMANGIOMA EXTENDING INTO THE HYPOTHALAMUS

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The association of facial and intracranial hemangiomas has been observed fairly often—82 cases having been reported up to 1936 (Greenwald and Koota[13])—but extension of a facial hemangioma into the intracranial cavity is indeed rare. An infant, in whom a facial hemangioma entered the intracranial cavity by way of the internal auditory canal, is the subject of the present paper. Such an extension of the tumor alone would make the case noteworthy, but the further spread of the tumor to the hypothalamus and the development of hypothermia and an increase in the concentration of serum magnesium are points of even greater interest. Hypothermia, associated with tumor of the hypothalamus has been observed (Ratner,[23] Cushing,[8] Obregia, Dimolesco and Constantinesco,[21] Foerster,[10] and Davison and Selby[9]), but an increase in the concentration of serum magnesium in such circumstances has, to our knowledge, not been previously reported.

Case Report. The patient, a white female infant, was born on April 6, 1939. Jaundice, present at birth, persisted for about 3 weeks. When the infant was 10 days old, a small pink papule was observed on her left cheek. The papule rapidly enlarged, assuming a purplish-red color, and by the time the infant was 12 weeks old, had spread over the upper left cheek, the left ear and postauricular area, and the left side of the scalp. It bled readily when rubbed, or otherwise traumatized. Irradiation of the area failed to check the growth. During the 12th week of life a thrush infection of the nose and pharynx developed and the infant had difficulty in swallowing and breathing. Occasionally she was apneic for as long as 30 seconds.

On June 29 the infant, then 12 weeks old, was admitted to the hospital of the University of Pennsylvania, on the service of Dr. J. C. Gittings. Her rectal temperature was 98.5° F. The hemangiomatous lesion on the left side of the face and head was widespread (Fig. 1). Examination of the eyes revealed nothing of significance except a persistent pupillary membrane on the right; the fundi showed no vascular abnormalities. Laryngoscopic examination disclosed a small, flat, soft purplish-red mass in the left piriform sinus and pharynx which was most prominent near the opening of the Eustachian tube. Roentgenograms of the skull revealed no evidence of intracranial calcification or demineralization of the calvarium. A small area of increased density in the right upper lung, which was ascribed to atelectasis, was the only abnormality observed in roentgenograms of the chest.

Fig. 1.—Photograph showing the extent of the hemangioma.

Examinations of the blood yielded the following values: hemoglobin, 10 to 8.4 gm. per 100 ml.; erythrocytes, 3.8 x 10^6 per c.mm.; leukocytes, 6 to 21 thousand per c.mm. (35% neutrophils, 54% lymphocytes, 11% monocytes). Urinalysis on several occasions was negative except for traces of albumin and occasional hyaline casts. Serologic tests (Kolmer and Kahn) were negative.

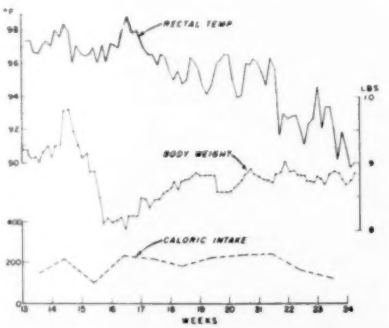

FIG. 2.—Rectal temperature, body weight and caloric intake during stay in hospital.

The essential clinical features during the last 11 weeks of life are illustrated in Figure 2. The rectal temperature was subnormal practically throughout the entire period of observation. During the last 4 weeks of life, the temperature ranged between 94° and 90° F., and on 2 occasions when a low registering thermometer was employed it was 88° and 89° F. On admission to hospital the infant's weight was 9 pounds, 3 ounces. During the 14th and 15th weeks of life diuresis developed and her weight decreased from 9.8 to 8.1 pounds. Following this drop there was a gradual increase in weight, the level at the time of death being 8.9 pounds. The infant's caloric intake was subnormal throughout the period of observation, the daily average being 189 calories (Fig. 2), which is about one-third of the estimated daily caloric requirement for a normal infant of the same age and weight. Although no estimation of the metabolic rate was obtained, it is evident that metabolism must have been very low, since after the 16th week the infant's weight increased even though the caloric intake was only a fraction of the normal requirement.

The results of analyses of the serum electrolytes are shown in Table 1. The serum was obtained from blood removed by cardiac puncture and collected under paraffin oil at the time of death. Since comparable normal values of magnesium and calcium were desired, analyses were made of the blood serum of 4 normal infants from 2 to 4 months of age. The results of these measurements are given in Table 2. When compared with the established normal values, the concentration of serum magnesium in our patient was increased 67%; serum calcium, on the other hand, was decreased 28%. Serum total base and chloride also were less than normal.[24] Serum inorganic phosphorus was increased 95% above Stearns and Warweg's[28] value for infants 2 to 4 months of age. The slight increase in $BHCO_3$ is in accord with the experimental data of Stadie, Austin and Robinson[26] which indicated an inverse change in bicarbonate of 1 mM per liter for every 4° to 5° F. change in body temperature at either constant CO_2 tension or constant pH.

Throughout the period of observation in the hospital, the infant was in a state of lethargy. She could be aroused sufficiently to take food but when her appetite was satisfied she soon lapsed into a semisomnolent state. Crying was rare. During the last few weeks of life a peculiar lardy, gelatinous appearance was evident. There was no visible edema. Death occurred on Sept. 17, 1939, in the 24th week after admission to hospital.

AUTOPSY (12 hours after death). *Gross Observations.* An enormous vascular tumor covered the greater part of the left side of the face, the entire left ear, the left temporo-occipital region of the scalp and the adjoining part of the neck. The growth, which was somewhat elevated above the surface of the skin, reached to the outer canthus of the eye but did not invade the eyelids. In the region of the ear it extended into, and partially occluded, the external auditory meatus. Reflection of the calvarium and dura revealed no abnormalities of the leptomeninges. On removal of the brain a moderately friable, somewhat lobulated, grayish-pink mass of tissue was found in the left cerebellopontile angle, where it was firmly adherent to the leptomeninges and indented the tonsil of the cerebellum and inferior portion of the pons. Laterally the mass was attached to the adjacent dura. It also filled the internal auditory canal and the middle ear, and was coëxtensive with the mass in the external auditory meatus.

In addition, a small portion of the tumor was found at the base of the brain, where it encompassed the hypophysial stalk and was firmly adherent to the tuber cinereum. Section of the brain revealed abundant tumor tissue within the fourth ventricle, continuous with that in the cerebellopontile angle. The entire ventricular system was moderately dilated.

The thoracic and abdominal viscera appeared normal except for patchy consolidation of the lungs.

and each lobule was surrounded by a zone of dense collagenous tissue of varying width. Within the fourth ventricle, most of the lobules were covered with a single row of cuboidal cells resembling ependyma (Figs. 3, *A*, and 4, *B*). The entire intracranial portion of the tumor was regarded as a malignant hemangio-endothelioma.

The mass in the left cerebellopontile angle surrounded and invaded the acoustic (Fig. 3, *B*) and adjacent cranial nerves to a variable degree, causing moderate degenerative

TABLE 1.—SERUM ELECTROLYTES IN INFANT WITH HYPOTHERMIA

Components	Values	Deviation from normal
Total base	138 mEq per L.	Decrease
Calcium	4.1 mEq per L.	Decrease
Magnesium	3 mEq per L.	Increase
Chloride	93.7 mEq per L.	Decrease
Total CO_2	66 vol. %	Increase
$BHCO_3$	28.1 mM per L.	Increase
Inorganic P	12.3 mg. per 100 ml.	Increase
BPr*	10.2 mEq per L.	Decrease

* BPr = 0.97 (Pr) (pH—5.26) where Pr = gm. protein per 100 ml. Serum protein = 4.9 gm. per 100 ml. and pH is assumed 7.4.

TABLE 2.—SERUM ANALYSES IN 4 NORMAL INFANTS, AGED 2 TO 4 MONTHS

Subject	Calcium (mEq per L.)	Magnesium (mEq per L.)
Web	5.9	1.98
McL	5.8	2.02
Bern	5.8	2.05
Nel	6.0	2.12

Methods. The brain stem was removed *en masse* and divided into 3 blocks. Each was embedded in paraffin, serially sectioned at 8 microns, and every tenth section stained with hematoxylin and eosin. The diencephalon and adjoining midbrain were sectioned in the horizontal plane, and the remainder of the brain stem transversely.

Microscopic Findings. The tumor in the scalp consisted of myriad well-formed capillary channels supported by fibroblastic tissue. The lumens of the channels were lined by a single layer of flat and evenly distributed endothelial cells. No mitotic figures were observed. Histologically, the picture was that of a benign hemangioma. In the intracranial part of the tumor (Fig. 3) the capillary channels were relatively less numerous, the main bulk of the tissue being composed of spindle-shaped cells of indefinite outline, with homogeneous cytoplasm and irregularly elongated, finely chromatic nuclei. There were moderate numbers of mitotic figures. The tumor was lobulated,

changes as manifested by proliferation of the endoneurium and the sheath cells of Schwann. The tumor in the cerebellopontile angle was continuous through the foramen of Luschka with that in the fourth ventricle, and a part of the tumor had broken through the tela choroidea and proliferated extraventricularly (Fig. 4). Examination of serial sections revealed that the intraventricular portion of the tumor extended from the midpontine region to the level of the decussation of the pyramids. The tumor had distended the fourth ventricle but had not invaded or visibly damaged the cerebellum, pons, or medulla oblongata, except for the ponticulus of the left side (Fig. 3, *A*), which was partially disintegrated. The tufts of the choroid plexus were displaced by the tumor but otherwise appeared normal. The area postrema showed no visible abnormalities. A small portion of the tumor had reached the right cerebellopontile angle (Fig. 4). No tumor tissue was observed in the region of

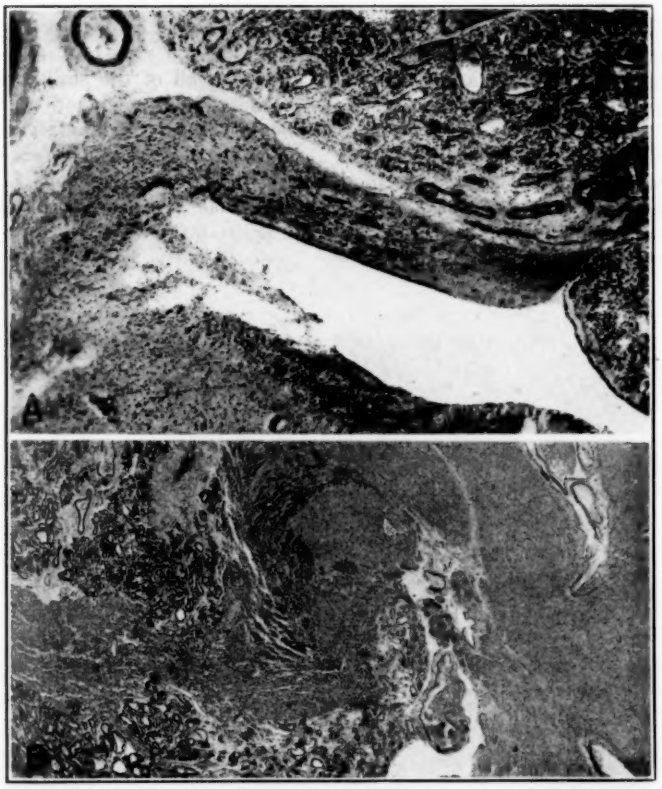

FIG. 3.—Intracranial portions of the tumor. In *A*, from the region of the fourth ventricle, tumor masses are attached to the inferior and superior aspects of the roof of the fourth ventricle respectively. The tissue surrounding the fourth ventricle has a normal appearance except at the lateral angle of the ventricle where the base of the ponticulus is partially disintegrated. × 90. (AIP Neg. 95106.) In *B*, from the region of the cerebellopontile angle, the tumor surrounds and partially invades the acoustic nerve. × 30. (AIP Neg. 95102.)

FIG. 4.—The medulla oblongata at the mid-olivary level. The main portion of the tumor is in the region of the left cerebellopontile angle, left foramen of Luschka, above the ventricular roof, and within the fourth ventricle. Bits of tumor evidently escaped from the right foramen of Luschka into the adjacent cerebellopontile angle. The tumor is decidedly nodular. The nerve in the lower left part of the photograph is probably the vagus or glossopharyngeal. × 10. (AIP Neg. 95095.)

the midbrain, nor was there any other abnormality aside from slight dilatation of the aqueduct.

Serial sectioning of the base of the brain was done in the horizontal plane, as mentioned previously. In the lowest section available, *i. e.*, at the level of the more inferior part of the optic chiasm and at the junctional zone between the neurohypophysis and the tuber cinereum (Fig. 5, *A*), the tumor had invaded and almost completely replaced the posterior and lateral walls of the uppermost portion of the hypophysial stalk as well as the median eminence and the adjacent retro-infundibular part of the ventromedial hypothalamic nucleus. The anterior wall of the stalk exhibited a mild proliferation of glia and a homogeneity of the perivascular glial sleeves. The encompassing pars tuberalis appeared normal. At a somewhat higher level (Fig. 5, *B*), the tumor had invaded and destroyed much of the retro-infundibular portion of the ventromedial nucleus. The uppermost extension of the tumor was at the level of the more superior part of the optic chiasm and the middle of the mamillary bodies (Fig. 5, *C*). Here the tumor was restricted to one side of the tuber cinereum, the ventromedial nucleus of which it had superficially invaded. A study of sections at higher levels disclosed degenerative changes in the paraventricular

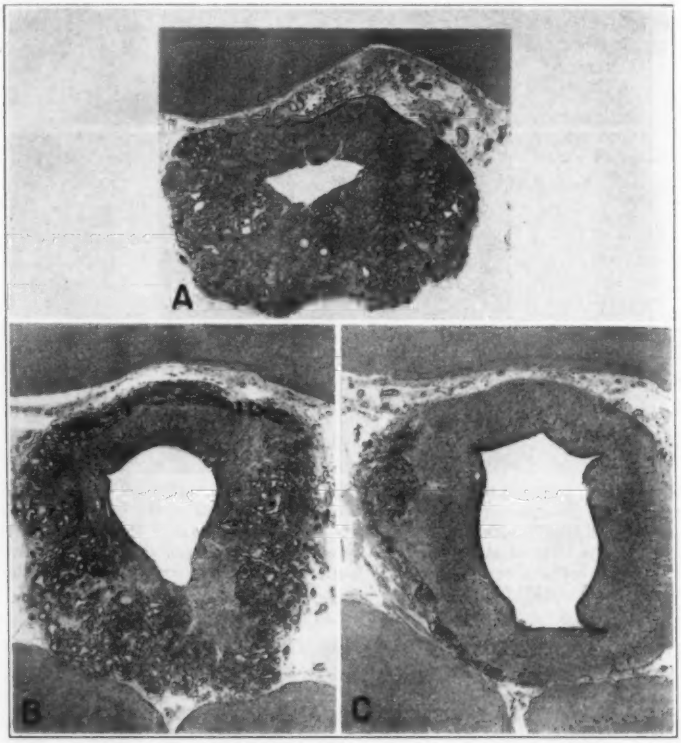

FIG. 5.—Horizontal sections through the base of the brain at the levels of (*A*) the lower aspect of the optic chiasma, (*B*) the mid-portion of the chiasma and the lower third of the mammillary bodies, and (*C*) the upper portion of the chiasma and the mid-region of the mamillary bodies. In *A* the tumor has destroyed the posterior and lateral walls of the infundibular stalk, the posterior part of the median eminence and the lowermost portion of the ventromedial hypothalmic nucleus. The infundibular recess of the third ventricle is visible. × 30. (AIP Neg. 95099.) In *B*, the ventromedial nucleus of both sides is virtually destroyed. (AIP Neg. 95107.) In *C*, the highest level at which the tumor grew, only the most lateral portion of the ventromedial nucleus is invaded. × 30. (AIP Neg. 95097.) At none of the levels are the optic chiasm (above) or the mamillary bodies (below) affected by the tumor.

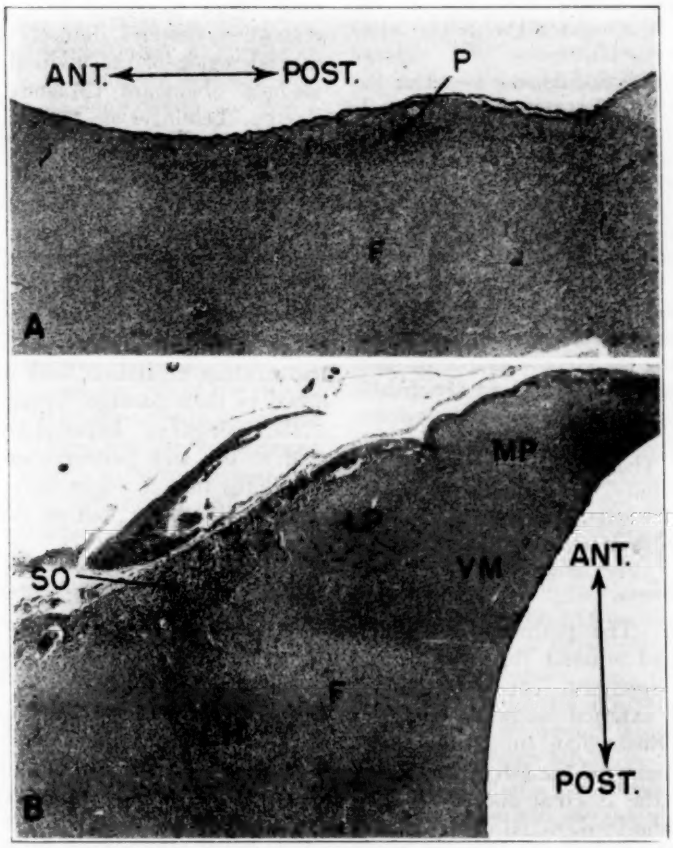

FIG. 6.—*A*, Horizontal section of the hypothalamus at the level of the mid-portion of the paraventricular nucleus (*P*). There is a moderate depopulation of the larger cells composing this nucleus. The third ventricle is dilated. The fornix (*F*) shows no change. × 30. (AIP Neg. 95101.) *B*, Dorsolateral part of the supraoptic nucleus (*SO*) shows a slight loss of ganglion cells. (At lower levels the ventromedial part of the supraoptic nucleus showed a greater reduction in cells.) No changes are visible in the ventromedial (*VM*), medial preoptic (*MP*), or lateral preoptic (*LP*) nuclei, or in the lateral hypothalamic area (*LH*) or the fornix (*F*). The third ventricle is dilated. × 30. (AIP Neg. 95098.) The arrows are included for purposes of orientation.

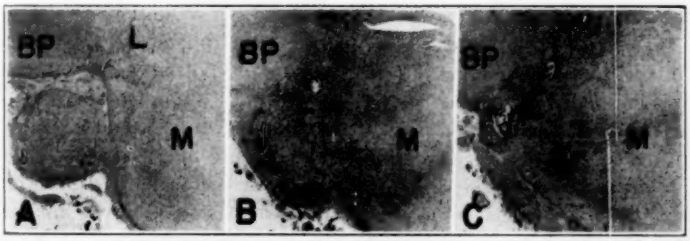

FIG. 7.—Caudal region of the hypothalamus (horizontal sections), showing a tumor nodule at 3 levels of the more inferior part of the mamillary body. In *A* the tumor is lateral to the mamillary body (*M*) and beneath the lateral hypothalamic area (*L*) and the medial aspect of the basis pedunculi (*BP*). In *B* it is adherent to, and invades superficially the lateral hypothalamic area, while in *C* it occupies a small circumscribed portion of the lateral hypothalamic area. In *B* and *C* a minor portion of the tuberomamillary nucleus has been replaced by the tumor. (AIP Negs. 95512–95514.)

and supraoptic nuclei, moderate in the former (Fig. 6, *A*) and slight in the latter (Fig. 6, *B*).

Another tumor nodule was found in the region of the posterior part of the hypothalamus (Fig. 7). It was small, had proliferated in the meninges just lateral to the mamillary body, and had invaded the more inferior part of the lateral hypothalmic area. Only a moderate number of cells of the tuberomamillary nucleus had been destroyed. The lateral mamillary nucleus and the nucleus intercalatus were unaffected.

Study of the other nuclei of the hypothalamus, including the preoptic, suprachiasmic and lateral tuberal, revealed no abnormalities. The optic chiasma was free from change. The remainder of the brain also was normal. The pituitary gland was not available for study. Of the other endocrine glands, only the adrenal and pancreas were sectioned. Neither showed abnormalities. Sections from the lungs disclosed acute lobular pneumonia.

Discussion. The pathway by which the tumor had entered the intracranial cavity was apparent. It had spread through the external auditory meatus, middle ear, Eustachian tube, and obviously had penetrated the labyrinth, for it had reached the internal auditory canal and entered the intracranial cavity along the course of the acoustic nerve. Proliferating in the region of the left cerebellopontile angle, it had traversed the adjacent foramen of Luschka, then gained the fourth ventricle, from which a part of the tumor escaped to the region of the right cerebellopontile angle; in addition, fragments of the tumor had presumably been carried by the current of the cerebrospinal fluid to the base of the brain where they took root in the hypophysial stalk and adjacent tuber cinereum as well as in the caudolateral part of the hypothalamus.

In attempting to provide an anatomic basis for the hypothermia and the decrease in metabolism, only 2 regions come into consideration: the lower brain stem and the base of the hypothalamus together with the neurohypophysis. In regard to the lower brain stem, it is well recognized in experimental animals that hypothalamic fibers concerned with temperature regulation descend diffusely in the tegmental region of the midbrain, pons and medulla oblongata (Magoun,[20] Keller,[18] Beaton, Leininger and McKinley[2]), and the evidence indicates that the same is true in man (List and Peet[19]). Since in our case the pons and medulla oblongata were apparently unaffected by the tumor, except for the ponticulus which seems to be nothing more than a support for the attachment of the choroid plexus, it may be assumed that fibers concerned with temperature regulation were not compromised in their passage through this part of the brain stem. Especial attention was paid to the area postrema owing to the possibility that it might have been damaged by the tumor, but no defect in this structure was observed.

It is necessary also to consider the possibility that the damage to the hypophysial stalk and median eminence may have given rise to the hypothermia and the reduction of metabolic activity. The lesion had destroyed the posterior wall and part of the lateral walls of the hypophysial stalk as well as the retro-infundibular portion of the median eminence. In experimental animals such as the rat, neither hypothermia nor a significant decrease in the rate of basal metabolism occurs after section of the hypophysial stalk (Anderson[1]). A persistent increase of 0.5° to 1° C. in body temperature was observed in dogs in which the hypophysial stalk had been sectioned, temperature regulation being otherwise unaffected (Hemingway, Rasmussen, Rasmussen and Wikoff[16]), but it is quite possible that during operation the adjacent anterior hypothalamic region was injured. Following hypophysectomy, the basal metabolic rate is reduced, and the body temperature may show a tendency to fall, but there is never the degree of hypothermia which was observed in our case. In 34 hypophysectomized dogs studied by Solari[25] the body temperature was within the normal range in 31; the remaining 3 had a mild degree of hypothermia, which was ascribed to damage incurred by the

tuber cinereum at the time of operation. In 2 other dogs in which the tuber cinereum was cauterized after hypophysectomy, the body temperature fell markedly, in 1 instance reaching 90.5° F. From these considerations it appears highly unlikely that the lesion responsible for the hypothermia in our case was in the neurohypophysis. Unfortunately the adenohypophysis was not available for study.

The hypothalamus was the only other structure affected, and here the damage was restricted to the more inferior part of the ventromedial nucleus bilaterally and to a very small portion of the caudal part of the tuberomamamillary nucleus unilaterally. There was no morphologic evidence of injury to cells beyond the regions of tumor infiltration. Obviously the heat maintenance mechanism was functionally inadequate. It is conceded that this mechanism is situated in the more caudolateral part of the hypothalamus and that the mechanism for heat dissipation is predominantly anterior in location, *i. e.*, chiefly in the preoptic and supraoptic regions of the hypothalamus (Ranson,[22] and others). The ventromedial nucleus occupies a position midway between these 2 mechanisms, and forms the bulk of the more medial part of the tuber cinereum. That experimentally induced lesions of the tuber cinereum lead to hypothermia has long been known (Isenschmid and Schnitzler[17]) but usually such lesions involved both the medial and lateral portions of the hypothalamus. Blair and Keller[3] have been able to eliminate the thermogenic mechanism by destroying the gray matter of the caudolateral hypothalamus but the effective lesions always damaged parts of the tuber cinereum as well. The lateral part of the tuber cinereum has been regarded as of importance in temperature regulation by Clark, Magoun and Ranson,[6] but not the ventromedial nucleus, since body temperature remained virtually unaltered when it was bilaterally destroyed. Stoll,[29] on the other hand, adduced evidence that the medial hypothalamic region does play an important rôle in temperature regulation, but he could not limit such activity to any one nucleus. Our case would seem to provide compelling evidence that *the ventromedial nucleus is an essential part of the heat maintenance mechanism.* It is doubted that the small unilateral lesion in the tuberomamillary nucleus was contributory to the development of hypothermia since small hypothalamic lesions generally do not give rise to symptoms unless they are bilateral.

It was striking in our case that the metabolic level was lowered to such a degree that the body weight was maintained on a caloric intake considerably less than normally required. Experimentally induced lesions of the hypothalamus also have been shown to cause a fall in basal metabolic rate (Grafe and Grünthal,[12] Grünthal, Mulholland and Strieck,[14] Strieck, Grünthal and Urra,[30] Bloch[4,5]). Thus, in well-controlled experiments on cats in which the tuberal and adjacent regions were damaged bilaterally, and the pituitary body spared, Bloch[5] observed that the fall in basal metabolic rate was usually relatively greater than the fall in body temperature, and that oxygen consumption was sometimes decreased as much as 20 to 25% in the presence of a normal body temperature. From these observations Bloch concluded that though the hypothalamic mechanisms of temperature regulation and basal metabolism overlap anatomically they show a certain degree of independence functionally.

Owing to a similarity in our patient's behavior to that of an animal in hibernation, especial interest was attached to the 67% increase in serum magnesium. The increase in serum magnesium resembles that seen in certain species during hibernation, Suomalainen,[31] for instance, having observed a 70% increase in serum magnesium in the hibernating hedgehog. In hibernation the essential features are general torpidity, loss of temperature control, and quiescence of the sympathicoadrenal system as reflected by a decrease in adrenalin content of the adrenals, and

hypoglycemia (Suomalainen[32]). Efforts have been made to determine the factor or factors responsible for the increment of magnesium in the blood serum in hibernating as well as non-hibernating animals. Steadman, Ariel and Warren,[27] testing the effect of hypothermia on serum magnesium, found in rabbits in which the body temperature had been rapidly lowered to levels between 55.4° and 71.6° F., that the average increase in serum magnesium was 24%; they ascribed the increase in serum magnesium either to a cessation of kidney function, which may have prevented the excretion of magnesium, or to the cold state, which may have prevented its return to its storage sites, mainly the bones and muscles. Notwithstanding the lethargic pseudohibernation produced in these animals, it is well recognized that neither lowered temperature nor other environmental factor is a *sine qua non* for the development of true hibernation (Gorer[11]). Cleghorn,[7] for instance, has observed that marmots of the lower Adirondacks normally go into seclusion in September when the weather is warm and the food plentiful.

In viewing the various phenomena which go to make up the state of hibernation, one is struck most by the torpor. This condition is akin to sleep, for as Gorer[11] has remarked, "Anybody who has dealt with hibernating mammals must know that an animal so lethargic as to appear lifeless may be awakened if manipulated at all carelessly." The site in the central nervous system responsible for the rhythmicity with which sleep follows wakefulness is generally conceded to be the caudal hypothalamus and adjoining rostral midbrain. It seems logical to assume that the same may apply to hibernation, the essential difference between sleep and hibernation being in rhythmicity. It should be pointed out that man is capable of a certain degree of hibernation if Volkov's[33] report is true that peasants in the region of Pskov, Russia, spend most of the winter asleep before a fire, awaking only once a day to tend the fire and to eat a little bread. In our patient, whom we regard as having been in a state of pseudohibernation, the essential lesion was hypothalamic. One small unilateral lesion was in the region responsible for the maintenance of the sleep-waking rhythm, while the bulk of the lesion was but a short distance away. Whether the hypothalamus can be held responsible for shifts in magnesium, in order to modify the *milieu interne* and protect against an unfavorable environment, is a point still to be determined.

Summary. In a case of hemangioma of of the face which developed into a malignant hemangio-endothelioma and spread rapidly into the intracranial cavity, where it proliferated in the region of the cerebellopontile angle, fourth ventricle, and base of the third ventricle, there were persistent hypothermia, lowered metabolism, and increased concentration of serum magnesium—findings resembling those in normal animals during hibernation. The tumor had invaded and partially destroyed the posterior and lateral walls of the hypophysial stalk, the posterior half of the median eminence and the more inferior part of the ventromedial hypothalamic nucleus bilaterally, and a small area of the tuberomamillary nucleus unilaterally.

Conclusion. The symptoms in this case are to be ascribed to damage of the ventromedial nucleus and consequent interruption of fibers which descend the brain stem as part of the autonomic nervous system.

The authors wish to express their appreciation to Dr. Evelyn Anderson for her suggestions in the preparation of the manuscript.

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CLINICAL STUDIES OF THE PHARMACOLOGIC EFFECTS OF TETRAETHYL AMMONIUM CHLORIDE IN HYPERTENSIVE PERSONS MADE IN AN ATTEMPT TO SELECT PATIENTS SUITABLE FOR LUMBODORSAL SYMPATHECTOMY AND GANGLIONECTOMY

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Some patients with early essential hypertension and an occasional patient with malignant hypertension are improved dramatically by lumbodorsal sympathectomy and ganglionectomy. A reliable method for selecting those patients with arterial hypertension who are suitable for extensive sympathectomy has not yet been found. Of the wide variety of tests now under examination, none has more accurately predicted a good result than has the careful grading of the severity of the vascular disease (Page and Corcoran[7]). Those with minimal vascular disease and those with necrotizing arteriolitis seem most favorably influenced by operation.

The barbituric acid hypnotics do not primarily affect the sympathetic ganglia or the vasomotor nerves. It is therefore not surprising that, although they have received wide usage, tests employing hypnotics such as sodium amytal have been signally unsuccessful as methods of selecting candidates for operation.

The inadequacy of the present methods of selection has led to the continued search for one which would reproduce the results of sympathectomy by administration of a drug. Acheson and Moe[1] and Acheson and Pereira[2] reported that the tetraethyl ammonium ion depressed the function of the sympathetic ganglia in cats. Ing[4] and Ing and Wright[5] reported that of all the sodium salts tetraethyl ammonium ions had the least curariform activity. Lyons[6] made preliminary studies to ascertain whether tetraethyl ammonium bromide duplicated the results of sympathectomy in man, and would therefore be useful in patient selection. Their initial results were encouraging.

In this report of the effect of the tetraethyl ammonium ion on 16 hypertensive patients studied on the medical service of the Research Division of the Cleveland Clinic, the commercial bromide was converted into the chloride to avoid the sedative effect of bromide ions. Eleven of the patients had essential hypertension, 4 malignant hypertension and 1 chronic glomerulonephritis. Dr. W. James Gardner, Chief of the Neurosurgical Department, performed the Smithwick type of lumbodorsal sympathectomy on 12 of them.

Method of Study. Tetraethyl ammonium chloride solutions containing 100 to 150 mg. per cc. of saline were used after sterilization by Seitz filtration. Dosages which averaged 33 mg. (range 25 to 51) per kg. of body weight were given to the first 8 patients by intravenous infusion. However, the undesirable reactions were so alarming that in the next 8 patients doses of from 4 to 7 mg. per kg. of body weight were used. These were given by single intravenous injections.

The experiments were conducted as part of the studies made before hypertensive patients are subjected to operation. For comparative purposes, the results ob-

tained with the widely employed "sedation tests" are included.

All measurements of blood pressure were made in the supine position. Control values represent the average of measurements made twice daily during at least 7 days rest in bed and serve as a reference point for all results reported.

33 mg. per kg. The change in blood pressure began within 1 minute after injection and was maximal in 3 to 5 minutes. It was sustained for 10 to 15 minutes after which time it gradually returned to pre-injection levels (Chart 1).

The nature of the hypertension, its duration, etiology and severity bore no

TABLE 1.—RESULTS OF INTRAVENOUS INJECTION OF TETRAETHYL AMMONIUM CHLORIDE

No.	Control blood pressure (mm. Hg)	Control pulse rate	Dosage (mg./kg.)	Post-injection arterial blood pressure	Pulse rate	Fall in systolic pressure	Fall in diastolic pressure	Change in pulse
1	150/100	80	51	140/100	80	10	0	0
2	176/110	78	40	110/80	72	66	30	−6
3	260/150	120	31	230/140	140	30	10	+20
4	185/130	88	30	180/130	88	5	0	0
5	183/124	88	28	115/80	96	68	44	+8
6	220/134	84	28	145/80	80	75	54	−4
7	240/140	90	28	190/130	96	50	10	+6
8	200/130	80	25	125/70	88	75	60	+8
9	230/145	100	7	150/115	120	80	30	+20
10	180/110	80	6	110/70	120	70	40	+40
11	240/140	120	6	148/110	96	92	30	−14
12	200/130	100	4	190/140	100	10	+10*	0
13	190/120	140	4	140/90	120	50	30	−20
14	160/120	100	4	140/110	120	20	10	+20
15	220/140	100	4	200/150	120	20	+10*	+20
16	170/115	80	4	100/75	112	70	40	+32
Mean	200/128	96	18 8	151/104	103	49	24	+8

* + indicates blood pressure levels above control values.

Results. (*a*) EFFECT OF ADMINISTRATION OF TETRAETHYL AMMONIUM CHLORIDE ON ARTERIAL PRESSURE AND PULSE RATE Of the 16 patients who received intravenous injections of tetraethyl ammonium chloride, 14 exhibited significant reduction of blood pressure (Table 1). Nine of them showed a marked fall of blood pressure. In 7 of these 9, normal levels were observed within 5 minutes after injection. Five showed only a moderate drop of blood pressure (10 to 80 mm. Hg systolic and 10 to 54 mm. Hg diastolic). The mean change in pressure was 49 mm. Hg systolic and 24 mm. Hg diastolic. The magnitude of reduction of arterial pressure was not directly related to the size of dose. In 8 cases an average dose of 4.9 mg. per kg. of body weight produced a mean reduction in blood pressure of 52 mm. Hg systolic and 40 mm. Hg diastolic, compared with a mean fall of 47 mm. Hg systolic and 28 mm. Hg diastolic following an average dosage of

apparent relationship to the degree of fall in blood pressure, as shown by the fact that 1 subject with malignant hypertension and 1 with chronic glomerulonephritis had normal blood pressure levels after the injection of 28 mg. of tetraethyl ammonium chloride per kg. of body weight.

No constant effect on the pulse rate was observed. One subject experienced tachycardia which increased the pulse rate by 40 beats per minute, but psychogenic factors undoubtedly contributed. Three patients had no change in pulse rate, and 4 had slight slowing of pulse rate. In 8 there was an average increase of 17 beats per minute.

(*b*) OTHER EFFECTS OF TETRAETHYL AMMONIUM CHLORIDE (TABLE 2 AND CHART 2). A wide variety of pharmacologic effects was observed (Table 2). They increased in number and intensity with increasing amounts of the drug. The first phase of the reaction was characterized by mydriasis, ptosis of the lid and

numbness and tingling. Mydriasis was a constant finding in all 16 patients, and was associated with complete cycloplegia with doses greater than 10 mg. per kg. of body weight. The pupils responded readily to pilocarpine, but slowly to physostigmine whose action depends upon intact parasympathetic ganglia and the consequent liberation of acetylcholine. Some degree of ptosis of the lids was observed in 14 patients. It appeared early and was often extreme. It was not associated with enophthalmos, suggesting that paralysis of the levator palpebri superioris had occurred. Numbness and tingling immediately after injection was noted by 14 patients. Although most marked in the extremities, they were also experi-

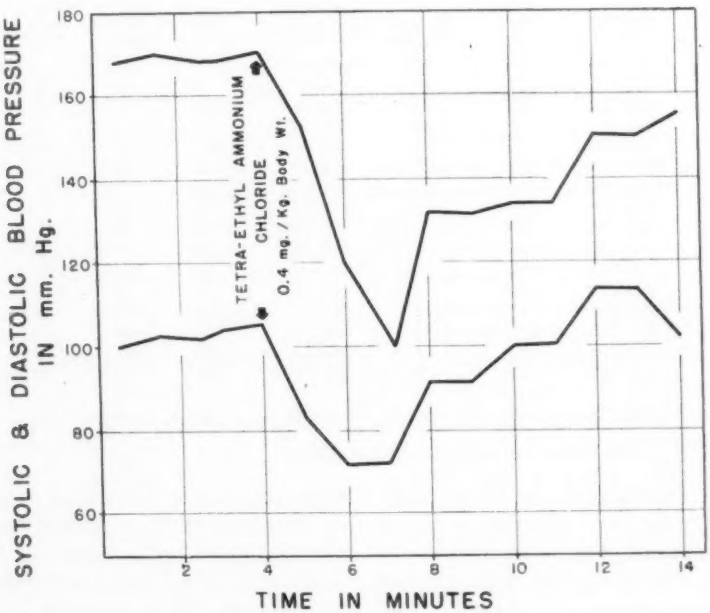


CHART 1.—Effect on the arterial blood pressure of the intravenous injection of tetraethyl ammonium chloride (0.4 mg. per kg. body weight).

TABLE 3.—EFFECTS OF INTRAVENOUS INJECTION OF TETRAETHYL AMMONIUM CHLORIDE, SODIUM AMYTAL SEDATION AND LUMBODORSAL SYMPATHECTOMY AND GANGLIONECTOMY ON ARTERIAL BLOOD PRESSURE

		Blood pressure					
		Following intravenous injection of tetraethyl ammonium chloride (mm. Hg)		Following sodium amytal sedation		Two weeks after lumbodorsal sympathectomy and ganglionectomy	
Patient	Control blood pressure (mm. Hg)	Lowest level	Degree of reduction	Lowest level	Degree of reduction	Average	Degree of reduction
1	150/100	140/100	10/0	120/70	30/30	120/84	30/16
2	176/110	110/80	66/30	156/100	20/10	140/90	36/20
4	185/130	180/130	5/0	150/110	35/20	180/130	5/0
6	220/134	145/80	75/54	154/100	66/34	220/134	0/0
8	200/130	125/70	75/60	180/116	20/14	200/126	0/4
9	230/145	150/115	80/30	140/100	90/45	210/130	20/15
10	180/110	110/70	70/40	130/90	50/20	194/118	+14/+8*
12	200/130	190/140	10/+10*	180/130	20/0	190/124	10/6
13	190/120	140/90	50/30	160/100	30/20	200/120	+10/0*
14	160/120	140/110	20/10	135/100	25/20	168/110	+8/10*
15	220/140	200/150	20/+10*	192/105	28/35	220/120	0/20
16	170/115	100/75	70/40	146/100	24/15	160/115	10/0
Average	190/124	144/101	46/23	154/102	35/22	184/117	7/7

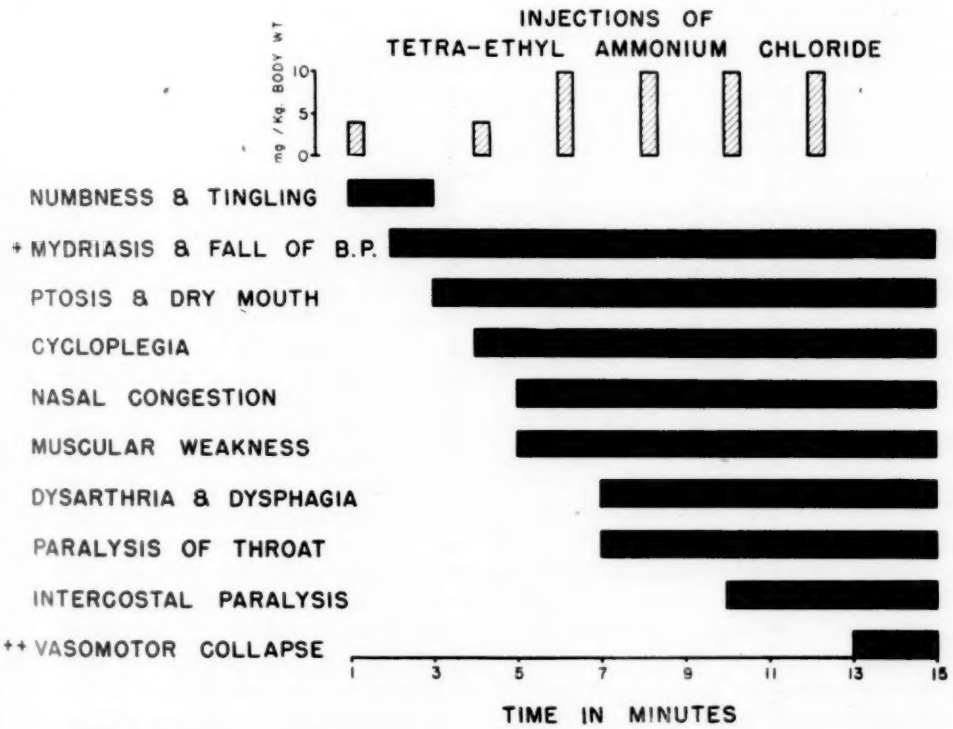
* + indicates blood pressure levels above control values.

enced in the tongue, where they were associated with an unpleasant metallic taste.

The second stage of the drug's activity, represented by dryness of the mouth and generalized muscular weakness, occurred in about half of the patients. Objectively the musculature was atonic and voluntary motion required much effort. The patients complained of lassitude and weakness. Nasal congestion was noted by 5 of them. It was apparently due to sympatholytic activity of the drug, since similar phenomena appear after bilateral stellate ganglionectomy.[3]

to complete inability to speak because of muscular weakness. Rest temporarily restored control but after a few words spoken with obvious effort, the patient was again inarticulate. Dysphagia had a similar progressive course, until the patient was completely unable to swallow. Concomitantly, respiration became difficult because of relaxation of the neck and throat muscles. In 1 patient respirations depended entirely upon diaphragmatic activity because of complete intercostal paralysis.

Following injection of 40 mg. per kg., 1 patient progressed rapidly through the



\+ NOT CONSTANT
++ OCCURED IN ONE PATIENT

CHART 2.—Illustration of the pharmacologic effects of tetraethyl ammonium chloride.

The third stage was experienced only by those patients who received intravenous infusions of large amounts of tetraethyl ammonium chloride. The manifestations seemed to be primarily curariform. Dysarthria appeared first. Speech was initially slow and studied; later it progressed above phases and developed complete circulatory collapse. He became cyanotic, lost consciousness and blood pressure and pulse were imperceptible. Voluntary respiration ceased. Artificial respiration, positive pressure oxygen administration, and intravenous injection of 2 mg. of

TABLE 2.—EFFECTS OF INTRAVENOUS INJECTION OF TETRAETHYL AMMONIUM CHLORIDE IN RELATIONSHIP TO DOSAGE

No.	Mydriasis	Ptosis	Numbness and tingling	Dry mouth	Generalized weakness	Nasal congestion	Dysarthria	Difficult respiration	Dysphagia	Vasomotor collapse	Asthma	Required intravenous prostigmine
					0 to 5 Mg. per Kg. of Body Weight							
1	.	++	++	+	+							
2	.	++	++	+	+							
3	.	...	++	+	+							
4	.	.	.	.	.	.	.	.	.	.	.	.
5	.	++	+	+	.	.	.	.	.	.	.	.
					6 to 10 Mg. per Kg. of Body Weight							
6	.	.	.	.	.	.	.	.	.	.	.	.
7	.	++	++	++	...	...	++					
8	.	++	++	++	.	.	.	.	.	.	.	.
					26 to 30 Mg. per Kg. of Body Weight							
9	.	.	.	.	.	.	.	.	.	.	.	.
10	.	++	++	++	+	+	+	+	+	.	.	+
11	.	++	++	++	+	+	+	+	+	.	.	.
12	.	++	++	++	+	+	+	+	.	.	+	.
13	.	++	++	++	+	+	+	+	.	.	+	+
					31 to 51 Mg. per Kg. of Body Weight							
14	.	++	++	++	+	+	+	+	+	+	+	+
15	.	.	.	.	.	.	.	.	.	.	.	.
16	.	++	++	++	+	+	+	+	+	+	.	.

prostigmine were necessary to save life. After 5 hours he seemed to have recovered, except that the blood pressure did not return to its previous hypertensive level until the next day. Three additional patients required intravenous injections of 1 mg. of prostigmine for the control of alarming toxic symptoms. Rhonchi were heard by auscultation in 2 patients. One developed a severe asthmatic attack which was relieved by intravenous administration of 0.5 gm. of aminophylline.

Chart 2 illustrates the approximate time of appearance and duration of symptoms and signs which develop after repeated injections of tetraethyl ammonium chloride.

(*c*) Comparison of Effects of Tetraethyl Ammonium Chloride, Sodium Amytal Sedation and Lumbodorsal Sympathectomy on Arterial Pressure in Hypertensive Patients. Twelve of the 16 patients were subjected to lumbodorsal sympathectomy. The blood pressure of each had been affected favorably by both tetraethyl ammonium chloride and sodium amytal sedation before operation (Table 3). The average fall in arterial pressure induced by each of these agents was 46 mm. Hg systolic and 23 mm. Hg diastolic and 35 mm. Hg systolic and 22 mm. Hg diastolic respectively. Two to 4 weeks after operation only 2 of these 12 patients had blood pressure levels measured at rest in the supine position that were lower than preoperative readings.

Discussion. If tetraethyl ammonium chloride had a highly selective depressing action on sympathetic ganglia, it should be possible to estimate pharmacologically the effect on blood pressure of lumbodorsal sympathectomy and ganglionectomy. This would provide a method for selecting candidates suitable for operation. However, the results presented indicate that in addition to its effect on the sympathetic ganglia it affects the parasympathetic ganglia, sensory nerve fibers and impairs motor function. Mydriasis and dry mouth represent inhibition of the parasympathetic components. All of our patients experienced some degree of numbness and tingling immediately following injection of the drug, suggesting that it acts upon sensory nerve fibers as well. Its curariform activity was indicated by dysarthria, dysphagia, ptosis and, finally, intercostal and diaphragmatic paresis.

A drug which acts so diffusely in human beings might be expected to affect the blood pressure in a manner different from that of sympathectomy and ganglionectomy. That this is true is indicated by the fact that the degree of arterial pressure reduction induced by tetraethyl ammonium chloride bears no relationship to that following sympathectomy.

Summary. Eleven patients with essential hypertension, 4 with malignant hypertension and 1 with chronic Bright's disease were given intravenous injections of varying amounts of tetraethyl ammonium chloride to determine whether the reduction of blood pressure induced by this drug had any relationship to the effect of lumbodorsal sympathectomy on arterial pressure. Fourteen of the 16 patients had appreciable reduction of blood pressure after tetraethyl ammonium chloride as well as after the sodium amytal test. Twelve of these were operated upon, but only 2 of them had any significant change in resting supine blood pressure measurements 2 to 4 weeks after operation.

The pharmacologic effects of tetraethyl ammonium chloride can be attributed to relative depression of the autonomic nervous system, stimulation of the peripheral sensory nerves and curariform action. The effects of the drug increased in number and in severity with the size of the dose. Fall of arterial pressure, mydriasis, peripheral numbness and tingling and ptosis of the lids appeared first. During the next stage the mouth became dry and muscular weakness and nasal congestion

appeared. Finally, curariform effects became pronounced and led to dysarthria, dysphagia and intercostal paralysis. One patient developed vasomotor collapse, unconsciousness and apnea, but recovered after treatment.

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THE ROLE OF TRAUMA AS A POSSIBLE ETIOLOGIC FACTOR IN REGIONAL ENTERITIS

THE EFFECT OF NON-PENETRATING TRAUMA ON THE SMALL INTESTINE OF DOGS

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AND
ALTON OCHSNER, M.D.†

THE etiologic importance of trauma in regional enteritis is a controversial subject. Most authorities are inclined to discount its importance.[3,9]

One of the cases seen by us, recently, aroused our interest in this subject.[12] A young soldier developed a regional enteritis confined to the proximal jejunum several months after a non-penetrating injury to the abdomen had been received in a motorcycle accident. A few other cases have been reported in the literature, in which there is a precedent history of trauma, and its etiologic importance is implied.[2,7,8,10] These cases are very rare, however, and no proof exists that the trauma was the causative agent. In discussions of trauma to the abdomen, in general, little emphasis is placed on non-penetrating trauma, unaccompanied by intestinal perforation or severe hemorrhage.[4,5,6,11,13] Experimental studies dealing with this subject are likewise scarce. Among these should be mentioned the negative report by Bell,[1] who found that interference with the blood supply of the intestinal tract does not result in a cicatrizing enteritis. Reichert and Mathes[10], however, succeeded in producing cicatrizing lesions of the small bowel by obstructing the mesenteric lymphatics with sclerosing agents.

We were interested in determining what effect crushing trauma, short of perforation, would have on the small intestine. The dog was chosen as the experimental animal, chiefly because of its size. This feature simplified the experimental problems. We were, of course, aware of the great resistance to infections of the dog's peritoneum, as compared with that of a human being.

Experimental Procedure. Adult mongrel dogs were used, varying in size between 7.5 and 23.0 kgms. The dogs were anesthetized with intravenous nembutal. They were not fasted the day of the operation. It was felt that the presence of rough food particles and a changed intestinal flora during digestion and absorption may enhance the effect of the trauma. The peritoneum was entered through a median or perimedian incision. A 10 cm. (approximately) segment of the jejunum and ileum was isolated and traumatized.

The trauma was produced by a special corrugated steel clamp. The screws were tightened as tightly as possible, and immediately released. This was done in order to simulate the momentary trauma usually involved in the production of abdominal injuries. The injured intestinal segments were immediately replaced in the peritoneal cavity, and the animal returned to the cage, after closure of the abdominal wall. Food was not withheld.

The animals were observed for appetite, vomiting, and the character of the stool, especially with regard to consistency, and presence or absence of blood.

Most of the animals were sacrificed 3 to 7 months after exposure to the trauma. During the early part of the experiment, abdominal exploration in the anesthetized animal was attempted, but this procedure was abandoned because it yielded insufficient information.

On autopsy, the gross appearance of the

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bowel and mesentery were noted, and sections were taken of the bowel and regional lymph nodes for microscopic examination.

Results. *Immediate Results of Trauma:* As was pointed out above, the clamp was applied momentarily, and in the process, about 8 to 10 cm. of ileum and jejunum were crushed. Upon removal of the clamp, the central portion of the compressed bowel was pale and ischemic. The antimesenteric side showed numerous hematomas. At various points on the antimesenteric side, the serosa and muscularis were split, with a resultant herniation of the mucosa. Hematomas were produced on the mesenteric side and in the adjacent mesentery as well, but the intestinal wall usually remained intact at this point (Fig. 1).

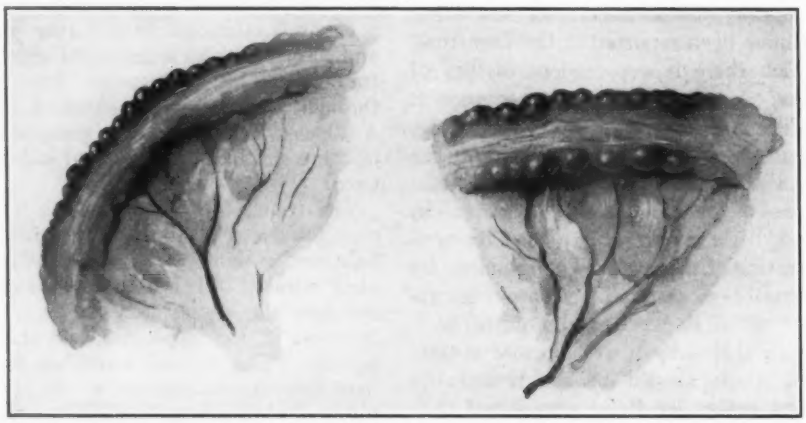

FIG. 1.—Appearance of bowel immediately after crushing injury. Note the splitting of the muscularis with herniation of mucosa and hematoma formation.

General Condition of the Animals: The animals commenced eating well shortly after surgery. Although some loss of weight did occur in most animals, this was not great (1–2 kgms.). All the animals retained their interest in food. No vomiting was noted.

The bowel movements were generally unchanged. But on several occasions, loose stools were noted, and a few times, gross blood was seen in the stools.

Gross Appearance: The most conspicuous gross finding was the distortion of the bowel by fibrous and omental adhesions (Fig. 2). The omentum and vascular adhesions appeared to attach themselves to the injured bowel, especially on the anti-mesenteric side. These adhesions matted together the injured segments, attaching them to other parts of the bowel, the abdominal wall, and solid viscera. In spite of the presence of very sharp angulations, there was no evidence of serious interference with bowel lumen. Small areas of apparent thickening of bowel wall, chiefly due to invagination, were noted, but concentric hypertrophy with significant interference with the calibre of the lumen was not seen.

The regional lymph nodes were enlarged. This was more marked in the ileo-cecal mesentery. In the living anesthetized animal, these adhesions, and hypertrophied lymph nodes, formed an extremely vascular granuloma-like mass, which bled profusely when disturbed.

The intestinal mucosa appeared intact grossly, with one exception—where a small shallow depression was seen, which appeared to be a superficial mucosal ulcer.

Microscopic Appearance: The mucosa itself was not involved. The glands were intact, and no true ulcerations were observed. In the submucosa, an abnormal accumulation of round cells was encount-

ered. This cellular exudate consisted chiefly of lymphocytes, some polymorphonuclear leucocytes, and an occasional eosinophile. No giant cells were seen (Fig. 3). The lymph follicles seemed larger and more abundant than normal, and the accumulation of lymphocytes seemed to spread beyond the boundary of the follicle.

The submucosa seemed thickened occasionally. In some animals, much fibrous tissue was seen on the submucosa, and this fibrosis seemed to spread into the muscularis. The injured area appeared to heal by fibrous tissue replacement and in one dog (Fig. 4), the muscularis was replaced by fibrous tissue running in different directions in an irregular manner.

In other instances, complete disruption of muscularis resulted in no fibrous tissue

FIG. 2.—Gross appearance of the bowel several months after injury. Adhesions and kinking of bowel are marked.

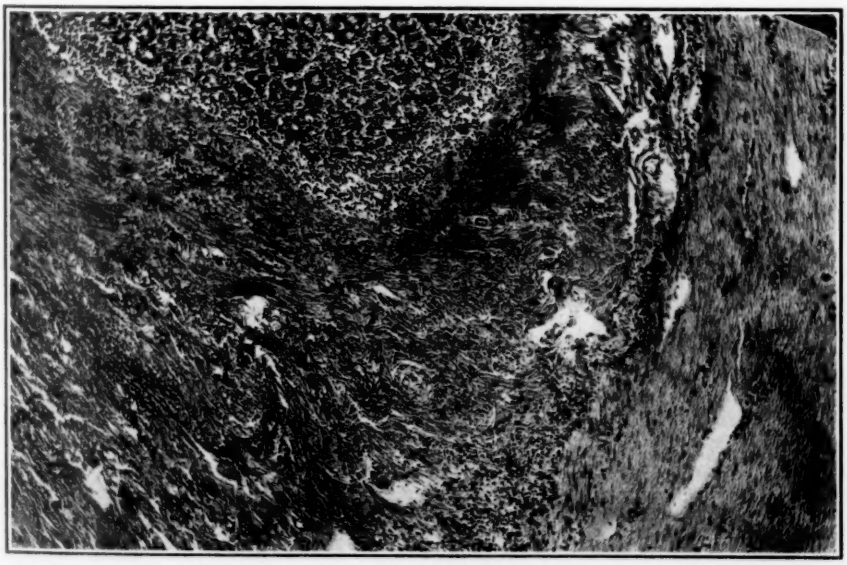

FIG. 3.—Accumulation of round cells in submucosa, and muscularis mucosae. × 50.

replacement, and the mucosa and submucosa were lying adjacent to the serosa. In this case (Fig. 5), no muscularis was seen in certain segments of the bowel.

The most conspicuous change seen in the serosa consisted of newly formed capillaries and round cell infiltration consistent with newly formed granulation tissues

FIG. 4.—Fibrous tissue replacement of muscularis and fibrosis of submucosa. × 50.

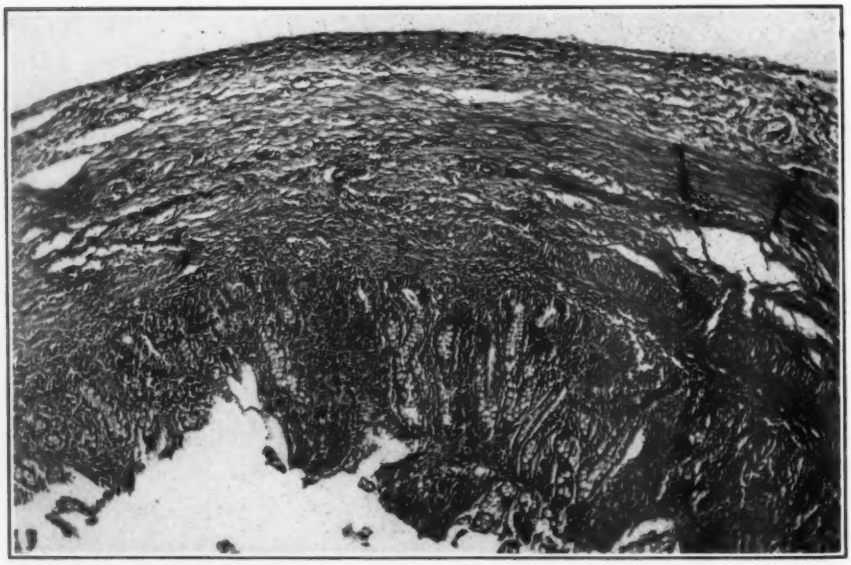

FIG. 5.—Complete absence of muscularis. The mucosa rests on serosa. × 100.

(Fig. 6). Infrequently, a foreign tissue reaction was seen in the serosa, and in such areas, an occasional giant cell was seen.

Discussion. In human beings, abdominal trauma, which is not productive of severe hemorrhage or immediate perforation of a hollow viscus, is not looked upon as a serious lesion. The immediate post-traumatic period is observed with anxiety, but when this period passes uneventfully, later complications are rarely thought of. When abdominal symptoms recur after several months, the preceding trauma is apt to be overlooked as a factor of importance.

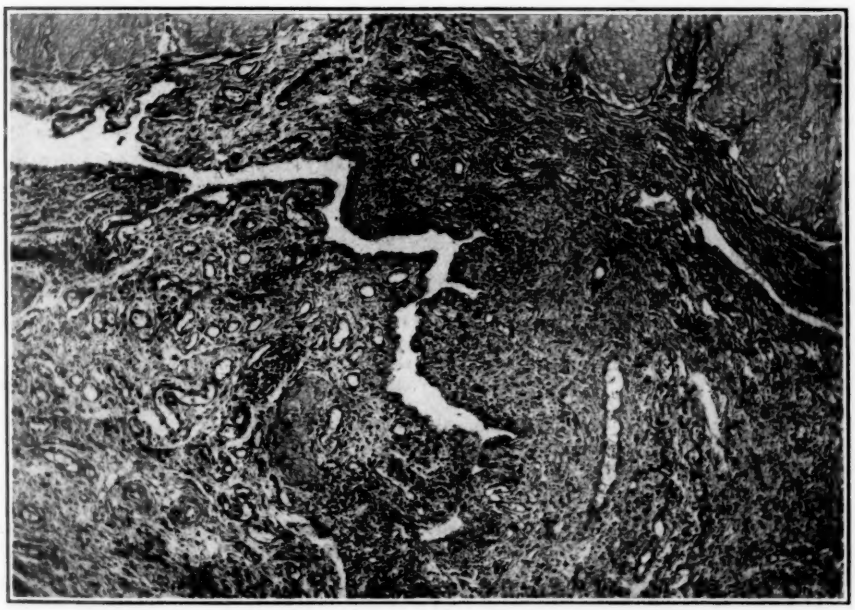

FIG. 6.—Newly formed capillaries and round cell infiltration in the serosa. × 100.

We succeeded in traumatizing severely the dogs' small intestines without producing gross perforation or severe hemorrhage. The immediate post-traumatic course was relatively uneventful. Later in the course of the healing of this trauma, there were no conspicuous objective signs, although it is possible that some subjective symptoms, such as pain, may have been experienced by the animals. The fact that all of them lost some weight suggests that the intake of food may have been limited by abdominal pain.

While the lesions seen did not simulate, either grossly or microscopically, those seen in regional enteritis, yet some features compatible with a chronic inflammation were present. Among these features may be mentioned the round cell infiltration, the fibrous tissue proliferation, and the new capillary formation seen in the serosa. The dissimilarity of this histologic lesion in the experimental animal from regional enteritis does not preclude the possibility that the healing process after trauma, in the human being, might produce changes similar to those seen in regional enteritis.

One thing seems obvious—that in the process of healing of non-penetrating and non-perforating intestinal trauma, long-lasting or permanent deformity of the bowel architecture may occur. Symptoms may not be produced till long after the injury, because as the healing process advances, more interference with the bowel lumen and motility may occur.

The fibrous tissue replacement of injured muscle fibers, or the accumulation of granulation tissue, may conceivably result in interference of motility and reduction of the bowel lumen. That this fibrosis in the muscularis and submucosa, seen in some of our animals, did not result in a narrowing of the bowel lumen and eventual stenosis is not unusual, when we remember that this injury did not involve equally the entire circumference of the bowel, but just one segment at a given level. It is conceivable, however, that with an appropriate combination of circumstances, a stenosis could be produced after many weeks or months; that is, after the fibrous tissue has had a chance to contract.

In spite of the fact that no obstruction or severe interference with the small bowel motility resulted from this injury, it is felt that, even in the dog, significant alteration in small bowel functioning was produced. And in human beings undergoing trauma of similar severity, the end results may be more serious, if the healing process is accompanied by more fibrosis and lymphoid tissue hyperplasia.

Summary and Conclusions: 1. Segments of ileum and jejunum were traumatized by crushing with a blunt instrument.

2. The animals survived the initial injury without ill effect.

3. Slight loss in weight and occasional loose or bloody stool was the only subsequent sign of derangement.

4. Animals sacrificed three to seven months later showed various gross and microscopic changes of a permanent nature in the injured bowel.

5. These changes, though not resembling those of human regional enteritis, exhibited some features compatible with a chronic inflammation.

The authors gratefully acknowledge the assistance given by Miss Rita K. Tortmase, R. N., in carrying out the surgical procedures.

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GENERALIZED CAPILLARY AND ARTERIOLAR PLATELET THROMBOSIS*

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Despite voluminous literature on the general subject of thrombosis, relatively few cases are recorded of a widespread thrombotic process limited exclusively to capillaries and arterioles. Such an unusual distribution of thrombi has been reported in only 10 cases[1,2,3,5,6,7,9] over a period of approximately 20 years. Clinically and pathologically these cases have been strikingly similar. In fact, the symptomatology has been so distinctive that the diagnosis may be made antemortem in the future. A rapidly progressing hemolytic type of anemia, a rather marked thrombopenia and bizarre nonlocalizing cerebral manifestations have constituted the salient clinical features. The course has been febrile, terminating in death in from 1 to 3 weeks. Widespread capillary and arteriolar thromboses have been the outstanding autopsy finding. Although Moschcowitz[7] regarded the thrombi as of the hyalin type, more recent writers[1,2,3,9] have considered them to be of platelet origin. Petechial hemorrhages have been repeatedly observed but the extent of these hemorrhages has varied considerably from one case to another.

Except for 1 previous case[9] and the one to be presented here, all of the patients have been females ranging in age from 9 to 66 years. The present case is reported in order to reëmphasize the rather uniform clinical pattern of this syndrome and the sequence of events incident to the underlying pathologic process.

Case Report. *History.* A 66 year old colored man was admitted to the U. S. Naval Hospital in a conscious but aphasic state. The history, as obtained from the patient's sister, revealed that he had been in good health until 2 days before admission at which time it was noted that his speech was inarticulate. On the day before admission, the patient could not be understood and could only mumble with considerable difficulty. He was unable to write with his right hand although he appeared to have full control of the arm. Drinking liquids became difficult and swallowing solid foods was impossible. The symptoms became progressively worse but from the onset the speech defect was of an intermittent character; on several occasions, a few clear words were spoken only to be followed suddenly by a series of inarticulate grunts.

The past history was essentially non-contributory as far as could be determined. He had suffered partial deafness for 20 years but had had no previous episodes of aphasia or dysphasia. A history of venereal disease could not be elicited and a detailed family history revealed no evidence of familial blood dyscrasias. There had been no exposure to or ingestion of drugs or poisons of any kind.

Physical Examination. The patient was a well-developed, well-nourished, colored male who was conscious, well oriented and coöperative but aphasic. The temperature, pulse and respirations were normal. The systolic blood pressure was 120 mm. of mercury and the diastolic 80 mm. The pulse rate was 84 per minute. Throughout his entire illness, the skin, scleræ, conjunctivæ and fundi revealed no evidence of petechial hemorrhages. The heart was not enlarged and there were no murmurs. The lungs were clear to percussion and auscultation. The abdomen was ovoid, non-tender aud no masses were palpated.

Bizarre and fleeting neurologic manifestations were of considerable clinical interest and importance. On admission, the only significant finding, aside from the aphasia

* This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the U. S. Navy. The opinions and views set forth in this article are those of the writer and are not to be considered as reflecting the policies of the Navy Department.

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and dysphasia, was diminished but equal strength of arms and legs. Four days later, however, the aphasia had cleared. Abdominal and cremasteric reflexes were absent bilaterally. The Achilles reflex was hypoactive on the right and absent on the left. Response to pain and touch was entirely absent in the lower extremities. Response to temperature changes in both upper and lower extremities was diminished. There was no muscular weakness. The following day, neurologic examination revealed agrammatism, acoustic and verbal agnosia, ideokinetic apraxia, increased spasticity and reflexes of the right arm with a positive Hoffman sign on the right. The patient was again sensitive to pain, touch and temperature in upper and lower extremities. Throughout the course of illness, these neurologic manifestations occurred in irregular cycles and appeared to wax and wane in intensity.

Laboratory Findings. The red cell count on admission was 1,800,000; hemoglobin, 38%; white cells, 7850 (70% polymorphonuclears, 20% lymphocytes and 3% monocytes). The red cells on direct smear showed marked hypochromia, anisocytosis, poikilocytosis and polychromia. There was 1 normoblast per 100 white blood cells. Other data: volume of packed cells, 20 per 100 cc.; mean corpuscular volume, 111.1 cμ; mean corpuscular hemoglobin, 30.6 $\mu\mu$g. and mean corpuscular hemoglobin concentration, 27.5%; volume index, 1.18; color index, 1.05; saturation index, 0.89. The reticulocyte count was 8.5%. A platelet count was not done but examination of the blood smear revealed a marked decrease of platelets. Following 2 whole blood transfusions, the red cell count rose to 2,300,000, with hemoglobin of 46%. The volume of packed red cells was 20%, with a mean corpuscular volume of 87 cμ. The mean corpuscular hemoglobin was 29 $\mu\mu$g. and the mean corpuscular hemoglobin concentration was 33%. The volume, color and saturation indices were, as before, within normal limits. The urine contained 3 to 5 red and white blood cells per H.P.F. and a trace of albumin was observed. A stool examination revealed no significant findings. A lumbar puncture revealed normal dynamics with no evidence of block on jugular compression. The white cell count was within normal limits and no red cells or xanthochromic fluid were observed. Spinal fluid glucose was 75 mg. %; chlorides, 766 mg. %; proteins, 35 mg.%. Serologic studies of blood and spinal fluid showed no evidence of syphilis. The icteric index was 13. A cephalin flocculation test was negative after 24 hours but showed 1+ after 48 hours.

Course. The patient was put on a high caloric diet and was given whole blood transfusions of 500 cc. each on 2 successive days. He appeared to improve physically but the mental status remained essentially unchanged. An intermittent fever ranging from 100° to 102° F. developed 3 days after admission and persisted throughout the remainder of his hospital stay. Five days after admission the patient developed urinary retention. Rectal examination failed to reveal an enlarged prostate gland or any rectal mass. The urea nitrogen was 42.8 mg. per 100 cc. with a CO_2 combining power of 38 vol. %. He became incontinent of urine and refused to eat. Coma developed rapidly and the patient expired 10 days after admission to the hospital.

Autopsy (12 hours after death). The body was that of a well-developed, well-nourished 66 year old Negro male, weighing 150 pounds and measuring 5 feet 7 inches in length. No marks, scars, rashes or hemorrhages were observed. The scleræ and mucous membranes were markedly icteric. There was no evidence of edema, engorged vessels or generalized lymphadenopathy. The pleural cavities were free of fluid but a few delicate adhesions were present in the left apex. The pericardial sac contained approximately 100 cc. of clear, straw-colored fluid. The organ relationships in the abdominal cavity were within normal limits.

The *heart* (335 gm.) showed many small epicardial and endocardial hemorrhages. The chambers were of normal size and they contained both fluid and clotted blood. The valve measurements were within normal limits and all valves appeared essentially normal. The cardiac musculature was muddy brown and flabby. On section, several small areas of hemorrhage, fibrosis and necrosis were present. The right and left ventricular walls were of normal thickness. The coronary arterial system showed moderate atherosclerosis but no thrombi were observed. The great vessels, except for moderate atherosclerosis, were not remarkable.

The combined weight of both *lungs* was

1050 gm. The external appearance revealed a smooth, mottled grayish red wet surface and crepitus was readily elicited. On section, a few small areas of grayish yellow consolidation were present in the left lower lobe. There was moderate congestion of the parenchyma throughout. The pulmonary vessels, bronchi and lymph nodes

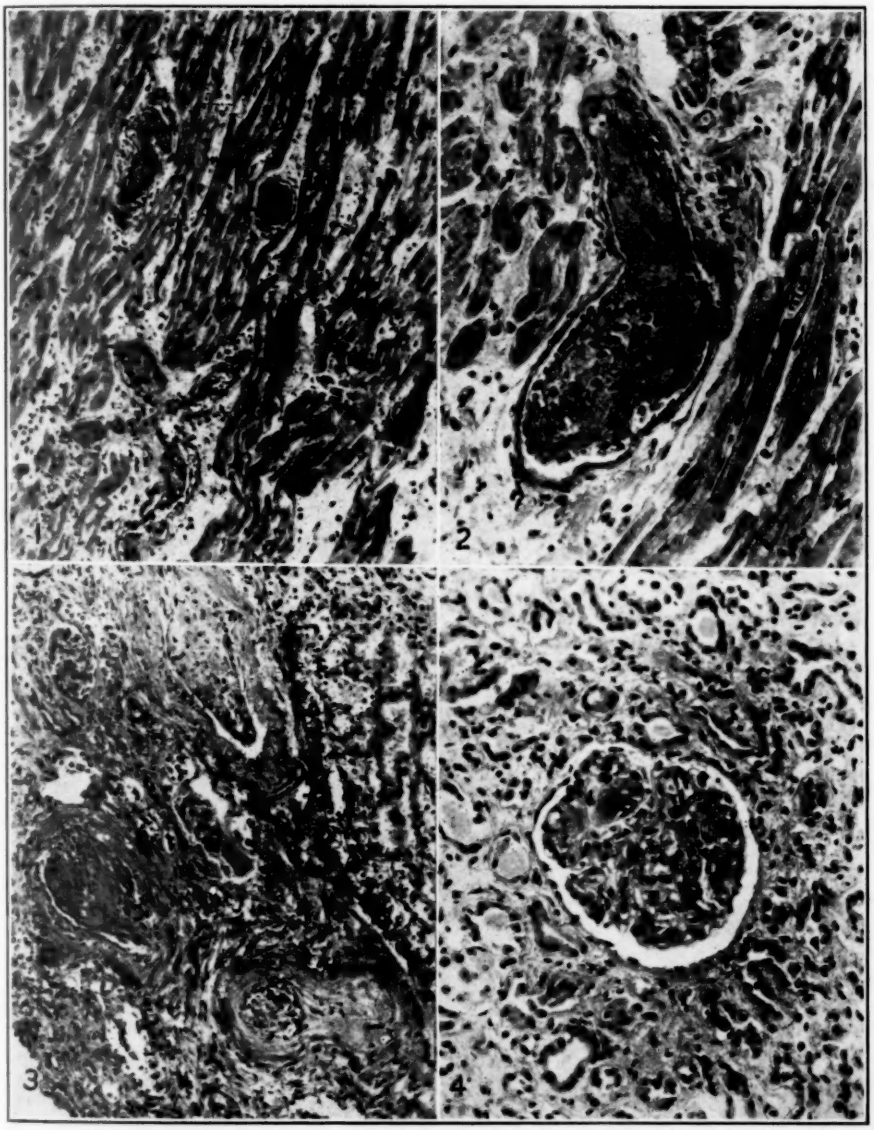

FIG. 1.—Section of myocardium showing thrombosis of capillaries with perivascular fibrosis, cellular infiltration and degeneration of adjacent muscle bundles. Hematoxylin and eosin; × 100.

FIG. 2.—A vessel in the myocardium showing invasion of a platelet thrombus by swollen endothelial cells. Hematoxylin and eosin; ×200.

FIG. 3.—Three vessels in the cortex of the kidney illustrating old dense endothelialized thrombi. Note the endothelial lined spaces bounded by the thrombi and the arteriolar walls. Hematoxylin and eosin; × 100.

FIG. 4.—Kidney showing platelet aggregates in glomerular tuft. Hematoxylin and eosin; × 200.

were not remarkable. The spleen (180 gm.) appeared essentially normal in size, shape and consistency. The pancreas, likewise, showed no significant abnormalities. The liver (1700 gm.) showed a surface everywhere smooth and intact, with the characteristic reddish brown color. On section, the architecture was well preserved but scattered throughout were numerous small petechial hemorrhages. The gall bladder and biliary tract were essentially normal. Multiple submucosal hemorrhages were observed in the stomach but the remainder of the gastro-intestinal tract was not remarkable. The adrenal glands were of normal size and although somewhat congested, showed no definite areas of hemorrhage.

The left *kidney* (160 gm.) and the right (170 gm.) were similar. The capsule stripped with ease revealing a smooth, reddish brown surface over which numerous small punctate hemorrhages were noted. On section, the cortex was of normal thickness but numerous hemorrhages and small areas of necrosis were observed. The pyramids were well developed and showed no significant abnormalities. The mucosa of the pelvis and calyces was markedly hemorrhagic but there was no evidence of erosion. In the lower pole of the left kidney was a well-circumscribed, firm, gray mass, 4 mm. in diameter. The ureters were slightly dilated and occasional small petechial hemorrhages were observed on the mucosal surfaces. The bladder was moderately dilated and the mucosal surface was markedly hemorrhagic. Multiple small abscesses were observed throughout the prostate and a small pocket of pus, approximately 1 cm. in diameter was present adjacent to the right seminal vesicle. The seminal vesicles, testicles and urethra appeared essentially normal. The skeletal system showed no significant abnormalities and multiple sections through the ribs and vertebra showed red, cellular marrow.

The neck organs were in no way remarkable. The *brain* weighed 1220 gm. The dura and leptomeninges were everywhere smooth and intact and there was no evidence of hemorrhage. The cerebral and cerebellar hemispheres exhibited the normal contours and the ventricular system was not dilated. There was no evidence of hemorrhage but occasional minute areas of softening were noted throughout the parenchyma. The basilar artery showed rather extensive thickening, tortuosity and atherosclerotic changes.

Postmortem Bacteriology and Blood Chemistry. Blood culture showed no growth; blood non-protein nitrogen, 205 mg. %; urea nitrogen, 103.8 mg. %; creatine, 4.6 mg. %.

Toxicologic Examination. Spectrographic analysis of liver and kidney tissue revealed no abnormally large quantities of any of the poisonous metals.

Microscopic Examination. Heart: The great majority of capillaries and arterioles were occluded with finely granular homogeneous material which had the appearance of conglutinated platelets. No red or white blood cells were noted nor was there any evidence of a lamellated pattern. The endothelial cells lining the occluded vessels were swollen and moderately pleomorphic. Proliferation of these cells was marked but only occasional mitotic figures were observed. In other areas, karyorrhexis and pyknosis of the endothelial cells were conspicuous. Many of these cells could be seen invading and encompassing the platelet thrombi. Many of the vessels were not completely occluded but showed small endothelial lined, crescent shaped spaces usually adjacent to the vessel wall. These spaces did not suggest recanalization but rather incomplete occlusion. Occasional vessels with no thrombi showed moderate swelling of the endothelial cells. In a few areas the vessel walls were ruptured allowing the thrombus material to exude into adjacent connective tissue and cardiac muscle. In some regions, the vessel walls had fused with the thrombotic material causing complete disintegration of the normal vascular architecture. Fibrinoid degeneration of the arteriolar walls was occasionally observed. Many of the thrombosed vessels were surrounded by cuffs of edematous fibrous tissue which contained numerous lymphocytes, plasma cells, histiocytes and occasional polymorphonuclears. No giant cells were present and the lesions bore no resemblance to Aschoff bodies. Many of the muscle cells adjacent to the thrombosed vessels showed degeneration and necrosis. Scattered diffusely throughout the interstitial tissue were small focal clusters of acute and chronic inflammatory cells. In such areas, the tissue was edematous and occasional small masses of fibrin were readily observed. Numerous small areas of infarction were present. Many of the infarcts were recent, while others showed

evidence of healing and fibrosis. The majority, however, were of the low-grade ischemic type. Moderate atheromatous changes were present in the coronary arteries, but no significant abnormalities of the endothelial lining were noted.

Lungs: Many of the alveoli were filled with acute inflammatory exudate. Congestion and edema were noted throughout. The bronchioles were choked with polymorphonuclears and fibrin. Several of the capillaries and arterioles were filled with platelet thrombi but the endothelial changes were not so striking as in the heart. Only an occasional megakaryocyte was seen.

Spleen: The pulp was congested and there was minimal hyperplasia of the Malpighian bodies. Many of the central arterioles and several of the smaller vessels in the trabeculæ contained platelet thrombi. A few megakaryocytes were seen but there was no increase of myeloid or erythroid elements.

Genito-urinary tract: Extensive vascular changes were observed. A few of the glomeruli were enlarged and showed increased cellularity. These hyperplastic changes were not striking and no fusion or crescent formation was observed. Many of the capillary tufts and the afferent and efferent arterioles were partially occluded by small granular platelet thrombi. The tubular epithelium in several areas revealed rather extensive degeneration and necrosis. Many of the tubules contained cellular débris and precipitated protein material. Hemosiderin pigment was present in rather large amounts in the epithelium of the collecting tubules. In areas, there was considerable interstitial fibrosis and scarring with distortion of the architecture. Several small wedge shaped hemorrhagic infarcts were observed in the cortex. The majority of the arterioles and capillaries were occluded with platelet thrombi. Fibrinoid degeneration of the arteriolar walls was conspicuous but there was no evidence of inflammation. The endothelial changes were quite similar to those observed in other organs. In addition, the arcuate and interarcuate arteries showed moderate intimal thickening and hyalinization. Large areas of hemorrhage were present in the pelvic mucosa and in the mucosa and submucosa of the ureters and bladder. Examination of the prostate gland revealed numerous confluent abscesses and a moderate degree of hyperplasia. Many platelet thrombi were scattered throughout.

Vertebral marrow: Sections showed numerous islands of erythropoietic tissue consisting largely of pronormoblasts and normoblasts. Cells of the myeloid series were represented in normal proportion. Megakaryocytes were abundant and in many areas there was a slight but definite increase of these cells. The character of the cytoplasm of the megakaryocytes was not distinct, even with Giemsa's stain, because of autolytic changes. Many of the capillaries contained platelet thrombi.

Brain: Scattered diffusely throughout were numerous intracapillary platelet thrombi. Occasional minute areas of encephalomalacia were encountered. No hemorrhage was observed but minimal neuronophagia was noted in some areas. Many of the non-occluded vessels showed abnormal fibrin threads. These threads were greatly thickened and some appeared to be hollow. These abnormal forms appeared to fuse, however, with the normal fibrin threads. Scattered throughout and adhering to the fibrin were small granular masses of platelets. In several of the partially occluded vessels, the thick fibrin threads had fused with platelets to form a homogeneous mass in which the fibrin structure barely could be discerned.

Other organs: Platelet thrombi and occasional areas of hemorrhage were observed in the pancreas, liver, adrenals, gastro-intestinal tract, lymph nodes, thyroid and pituitary glands.

The Thrombotic Lesion. All of the tissues examined revealed large numbers of thrombotic and endothelial lesions in the capillaries and arterioles. These vascular lesions were most marked in the myocardium, kidney cortex, adrenal glands, spleen and brain.

With the routine formalin-fixed hematoxylin and eosin sections, the thrombotic material appeared as a finely granular purplish pink substance that morphologically, at least, suggested platelet origin. In an attempt to determine the precise nature of the thrombotic material, Giemsa, Shorr, Gram-Weigert, iron hematoxylin and iron stains were carried out on formalin and Zenker fixed tissue. These additional staining procedures tentatively substantiated our original interpretation and those of others, that the capillary occlusions were probably

of platelet origin. Neither red cells, disintegration products of red cells, leukocytes or bacteria could be demonstrated in the capillary and arteriolar occlusions. The proliferation and swelling of the endothelial cells and the permeation of the thrombi by these cells was a most remarkable phenomenon. Although occasional non-thrombosed vessels showed minimal endothelial swelling and proliferation, the process was not diffuse; the overwhelming majority of the non-occluded vessels appeared essentially normal. Many of the non-thrombosed vessels contained serum and normal sized delicate threads of precipitated fibrin, but occasional masses of distinctly abnormal fibrin threads were also observed. These threads were 3 to 5 times the thickness of normal fibrin and had the appearance of hollow, non-segmented mycelia. That these bizarre shaped masses were not mycelia was ruled out on morphologic and cultural grounds. Except for the size, the morphologic characteristics and the staining reaction were those of normal fibrin. They were occasionally observed in the newly formed thrombi where platelet aggregates could be seen adhering to them.

Discussion. The genesis of the platelet thrombosis is not known. There is considerable divergence of opinion regarding the fundamental vascular lesion. Altschule[1] speculated that the platelet thrombi were secondary to damaged vascular endothelium. Baehr, Klemperer and Schifrin[2] and more recently Bernheim[3] felt that there was no definite evidence for primary endothelial damage and that the endothelial changes were secondary to the presence of platelet thrombi. Nothing is to be gained by further speculation over this somewhat controversial point on the basis of morphology alone. There are, however, in this present case 1 or 2 observations that are worthy of consideration. In several of the vascular lesions, particularly in the myocardium, the capillary and arteriolar walls revealed rather marked fibrinoid degeneration and actual necrosis with extrusion of the thrombotic material into the adjacent tissue. Whatever the nature of the toxic agent, if there is such, vascular damage was marked. Such changes occurred only in vessels which contained platelet thrombi. It is possible that the toxic agent could have been absorbed on the platelet aggregates and that the concentration of the "toxin" was, therefore, greater and more lasting.

Abnormal clotting of the blood is a further possibility which deserves serious consideration from the standpoint of etiology. Although there is no basis for assuming that a defect in the blood clotting mechanism may produce morphologic changes, the abnormal physical nature of some threads of fibrin is perhaps suggestive of such a defect. Regardless of this questionable evidence, there are a number of points in both the stoichometric and enzymatic phases of the clotting mechanism at which a disturbance of one or more of the components might occur. Excessive clotting as well as acceleration of coagulation is favored by factors which tend to increase the formation of fibrinogen, prothrombin or platelet factor. The stimulation of bone marrow activity with increased production of blood platelets is one such factor, although after a minimal number of platelets is available, this is a rather minor one. Excessive agglutination and disintegration of platelets might be attributed to excessive amounts of the factor deficient in hemophilia. On the other hand, a defect in the platelets may be a qualitative one, that is, a too ready release of thromboplastin from abnormal platelets showered into the blood stream from the bone marrow. Again the abnormal clotting may be due to an inadequacy of the normal antithrombin of the blood thus permitting traces of active thrombin to remain active. The thrombin itself may be abnormal in this regard. In some recent, but as yet unpublished work,[4] it was discovered that if thrombin be subjected to rather mild denaturation procedures, it becomes refractory to antithrombic activity and yet retains the ability to convert fibrinogen into fibrin. It is conceivable, therefore, that traces of thrombin formed in the blood stream from the conversion of prothrombin might be

altered in such a way that the thrombin no longer would be inactivated by antithrombin. Whether or not the vascular lesions are the result of endothelial damage or of some defect in the clotting mechanism, or both, it is undoubtedly true that other well-known mechanical factors play a rôle in the ultimate formation of the thrombi. Otherwise it would be difficult to explain the distribution of the vascular occlusions. The various possibilities suggested are, of course, purely speculative but it is strongly urged that the clotting mechanism be studied carefully when the opportunity presents itself in the form of another case.

As Baehr *et al.*[2] first suggested, the enormous numbers of platelets enmeshed in the thrombosed vessels throughout the viscera were indeed sufficient to have exhausted the available supply and to have resulted in the thrombocytopenia of the peripheral blood. In the case presented, there was not an excess of megakaryocytes in the lungs or spleen. The bone marrow, on the other hand, did show a slight but definite increase of megakaryocytes. In the majority of cases reported, the numbers of megakaryocytes in the marrow have been within essentially normal limits—as they are in most cases of idiopathic thrombopenic purpura.[10] The marrow responds to the peripheral thrombopenia by increased platelet production from preëxisting megakaryocytes and not necessarily from hyperplasia of megakaryocytes. There is no good evidence to indicate that increased platelet production did not occur in these cases. In fact, it probably did, but the increased production might well fall far below the number used up in the formation of the thrombi. This is certainly reasonable in view of the enormous extent of the capillary and arteriolar bed and the widespread distribution of the lesions. Therefore, there is no reason to assume a depression of platelet production or splenic destruction to account for the thrombopenia.[6]

It has been repeatedly observed, especially by Baehr *et al.*, and Altschule, that despite the extent of the thromboses, there was little evidence of parenchymal necrosis. In this case, although small areas of infarction were present in the heart and kidneys, the degree and extent of the necrosis were minimal when compared to the myriads of thrombosed vessels. We agree with Bernheim that the lack of significant necrosis may be attributed to incomplete occlusion of the involved vessels and to the lack of involvement of the total capillary bed in a given area. It was mentioned previously that small but definite endothelial lined spaces were present at the periphery of many of the thrombi. Such lesions did not have the appearance of recanalized vessels but suggested incomplete occlusion initially. Indeed, the histologic appearance of a large number of infarcts suggested a prolonged ischemic process indicative of slow or incomplete occlusion.

From a thorough study of the clinical and pathologic material in this case, it is felt that the syndrome is not related to lupus erythematosis disseminata, polyarteritis nodosa, or any of the other diseases of the erythema group. The patient in the case reported above showed no evidence of pericardial and pleural involvement, edema, lymphadenopathy, skin lesions, leukopenia and endocarditis commonly encountered in disseminated lupus. The purpura and the vascular lesions are insufficient criteria which do not justify the attempt to relate this syndrome to disseminated lupus.[6] Furthermore, the vascular lesions in both disseminated lupus and polyarteritis are considerably different from those observed in this case. Whereas the significant changes in lupus and polyarteritis are to be found in the walls of the blood-vessels, in the syndrome under discussion, platelet thrombosis is the most noteworthy observation. The perivascular inflammatory reaction is not generalized, and where present, it is essentially chronic. In their work on the response of tissues to bacterial filtrates, Shwartzman, Klemperer and Gerber[8] pointed out the similarity of the vascular lesions in

this syndrome to the alterations observed in the blood-vessels of animals in which the Shwartzman phenomenon had been induced.

Because of the widespread capillary and arteriolar thromboses, biopsy should be a useful adjunct in establishing the diagnosis during life.

Summary. A case of a 66 year old Negro male with marked anemia, thrombopenia and bizarre neurologic manifestations is described.

Generalized capillary and arteriolar platelet thrombosis was the outstanding postmortem finding.

The type and distribution of the vascular lesions are pathognomonic of the disease process and the clinical and pathologic features in the cases reported are strikingly similar.

The cause of the thrombosis is unknown.

Brief discussions of the possible etiologic factors and the differentiation from certain diseases of the erythema group are given.

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HYPOPROTHROMBINEMIC ACTION OF QUININE SULFATE

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The observation was reported by us[4] some time ago that quinine sulfate in single daily oral doses of 0.33 gm. induces hypoprothrombinemia which can be prevented by concurrent administration of vitamin K. However, Quick[6] found that this antimalarial caused no decrease in the prothrombin of the blood. Clark and Spitalny,[1] on the other hand, have recently presented their findings that quinine exhibits prothrombinopenic action. This discrepancy of results prompted us to investigate further the action of quinine on prothrombin activity.

Experimental. *Repetition of Previous Experiments.* Two more subjects were studied following the procedure outlined previously.[4] Again Russell viper venom "Stypven" was employed as the thromboplastic agent in performing prothrombin time estimations. Both persons responded to a daily dose of 0.33 gm. of quinine sulfate with a distinct prolongation of their respective premedication prothrombin times. Upon discontinuing quinine sulfate the findings approximated the original values promptly. Combined administration of a vitamin K compound (10 mg.)* with quinine sulfate (0.33 gm.) over the period of time in which the latter alone had produced the rise in prothrombin time, prevented the quinine-induced prothrombinopenia. Withdrawal of the vitamin K compound and continuation of quinine sulfate at the same dosage level again elicited a prolongation of the prothrombin time in both subjects.

Comparative Study With Different Thromboplastic Agents. The difference in Quick's and our procedure was that different thromboplastic agents were used in estimating prothrombin times: He employed a tissue extract from rabbit brain and we utilized viper venom. Hence a comparative study on the blood of the same persons was instituted using as thromboplastic agents, viper venom on the one hand and a tissue extract on the other.† The former was employed in accordance with the technique advocated by Page and his associates[3] and first described by Fullerton.[2] In carrying out the tests with the tissue extract Quick's original method was followed.

Five normal female subjects ranging in age from 23 to 65 were chosen. Their nutritional state was satisfactory and they were advised to maintain a well-balanced diet. For these persons, prothrombin time estimations were performed on 3 days, in each instance utilizing both viper venom and the thromboplastic tissue extract. Every test was carried out twice. Averages of the 6 values thus obtained in each case for either thromboplastic agent were calculated and taken for the premedication prothrombin time with that particular thromboplastic agent.

The duplicate assays done with a given thromboplastic material in the individual cases were in agreement within the limits of experimental error. However, as appears from Table 1, great variations were found in the prothrombin times obtained

* The vitamin K compound used in this entire study was 2-methyl-1,4-naphthohydroquinone-diphosphoric acid ester tetrasodium salt, Synkayvite "Roche."

† For the purpose of this comparison it seemed adequate to utilize one of the commercially available, standardized preparations derived from lung tissue.

for the same subjects by using the 2 different thromboplastic agents.

Each person received quinine sulfate in single daily doses of 0.33 gm. by mouth for periods varying from 4 to 11 days. Prothrombin times were estimated at frequent intervals, utilizing both thromboplastic materials in each instance. With viper venom, quinine-induced hypoprothrombinemia became evident after 4 to 9 days, but the corresponding tests performed with thromboplastic tissue extract did not indicate a change of prothrombin activity. Quinine medication was continued until the total intake amounted to 2.64, 3.63, 3.33, 2.97 and 1.32 gm. respectively. The corresponding prolongations of prothrombin time at the end of these courses are listed in Table 2.

TABLE 1.—PROTHROMBIN TIME WITH VIPER VENOM AND WITH TISSUE EXTRACT

Case No.	Subject	Prothrombin time using viper venom (sec.)	Prothrombin time using tissue extract (sec.)
1	G. L. G.	22.7	13.3
2	E. F.	21.3	13.0
3	E. N.	26.5	13.9
4	M. P.	24.4	13.7
5	E. L.	25.7	14.8

Means of control prothrombin times obtained in 5 subjects by using viper venom and tissue extract respectively as thromboplastic agents.

TABLE 2.—PROLONGATIONS OF PROTHROMBIN TIMES

Case No.	Total quinine sulfate intake	Prothrombin time prolongations (viper venom) (sec.)	Prothrombin time prolongations (tissue extract) (sec.)
1	2.64	12.3	0.7
2	3.63	9.7	0
3	3.33	6.5	2.1
4	2.97	4.4	1.1
5	1.32	10.6	0.2

Prothrombin time prolongations obtained in 5 subjects at the end of course of quinine sulfate administration, using viper venom and tissue extract respectively as thromboplastic agents.

Upon discontinuing quinine sulfate the raised prothrombin times promptly regressed and approximated the respective control values within a few days. Subsequently, each subject was placed on the combined oral medication of 0.33 gm. quinine sulfate and 5 mg. of a vitamin K compound daily (in Case 2 once 0.66 gm. quinine sulfate and 10 mg. of vitamin K were taken inadvertently). This dosage was continued at least over the period of time in which quinine sulfate alone had been taken. Prothrombin time estimations carried out at frequent intervals with both thromboplastic agents in general yielded values which for the individual persons ranged at the same levels recorded for them with the respective agent in the premedication control period.

The combined quinine sulfate-vitamin K medication was followed immediately by a third experimental phase in which vitamin K was withdrawn but quinine administration continued. Again all 5 subjects responded with another pronounced elevation of their prothrombin times when viper venom was used for performing the estimations, but they exhibited no change when thromboplastic tissue extract was employed.

The accompanying charts portray the experimental procedure, and the results obtained.

Discussion. The findings presented furnish evidence that a prothrombinopenic action of quinine is demonstrable if viper venom is employed as thromboplastic agent, but that no such effect becomes evident if instead, a fast-acting thromboplastic tissue extract is used. The readings obtained with the latter preparation are of the same order of magnitude as those recorded by Quick.[6] In the 4 sub-

jects he studied, the premedication prothrombin times varied from 11.5 to 12.5 seconds, and the corresponding findings for the 5 persons presented here ranged from 13 to 14.8 seconds, with readings during quinine medication never exceeding 16 seconds.

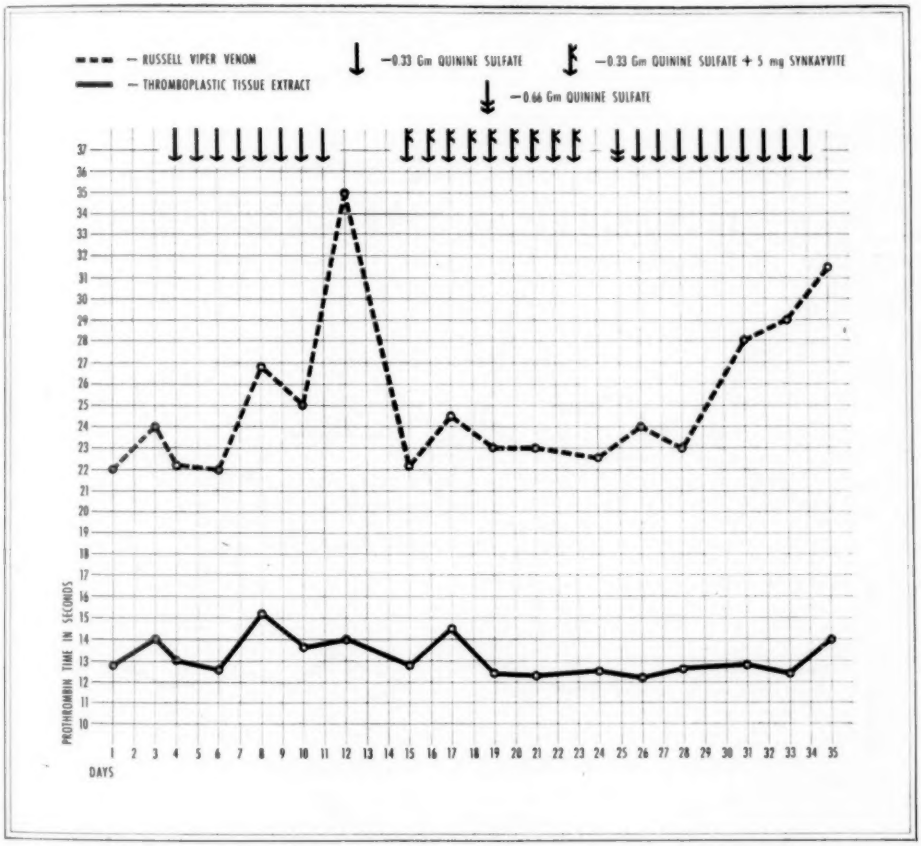
— RUSSELL VIPER VENOM
— THROMBOPLASTIC TISSUE EXTRACT
—0.33 Gm QUININE SULFATE
—0.33 Gm QUININE SULFATE + 5 mg SYNKAYVITE
—0.66 Gm QUININE SULFATE
PROTHROMBIN TIME IN SECONDS
DAYS

CHART 1.—Effects of quinine sulfate and of quinine sulfate in conjunction with Synkayvite on prothrombin time values obtained with Russell viper venom and a fast-acting thromboplastic tissue extract in G. L. G., a white female, aged 23. In this chart and in Chart 2 it is shown that quinine-induced hypoprothrombinemia is reflected if Russell viper venom is used as the thromboplastic agent, but it is not with a fast-acting thromboplastic tissue extract; concurrent vitamin K administration counteracts quinine-induced prothrombinopenia; continuation of quinine sulfate without vitamin K causes another rise of the prothrombin time if Russell viper venom is employed.

In contrast, premedication values obtained with viper venom in the same individuals varied from 21.3 to 26.5 seconds and showed elevations of as much as 12.3 seconds following the administration of quinine over several days. Such prolongations reflect a hypoprothrombinemic action of quinine. The protective effect of vitamin K against such quinine-induced prothrombinopenia becomes evident from the present findings and those reported previously.[4]

Quick in a recent paper[5] states with reference to his method of prothrombin determination that one "cannot detect changes until the prothrombin drops to 50%." This is apparently not so if in place of a fast-acting thromboplastin, an agent of lesser speed, such as viper venom, is used. Then also mild degrees of prothrombin depletion can be demonstrated.

Similarly, in experiments to be reported elsewhere it has been shown that the salicylate-induced hypoprothrombinemia becomes apparent if either viper venom or a slowly acting thromboplastic tissue extract is used but that no prothrombinopenia is demonstrable with a fast-acting thromboplastin. However, as will likewise be reported elsewhere, this fast-acting thromboplastic tissue extract reflected a more marked reduction in prothrombin activity in patients receiving dicumarol than did viper venom. Therefore, the possibility must not be overlooked that with different thromboplastic agents, different factors of the complex process of blood coagulation are affected. Notwithstanding, there can be no doubt that an elevation of the prothrombin time as observed with viper venom in persons receiving quinine sulfate reflects a prothrombinopenic state, owing to the fact that concurrent vitamin K medication invariably prevents a rise of prothrombin time.

Summary. Additional evidence is presented that quinine sulfate reduces prothrombin activity as gauged by the ensuing prolongation of prothrombin time if Russell viper venom is used as thromboplastic agent. Quinine-induced hypoprothrombinemia can be prevented by the concurrent administration of vitamin K.

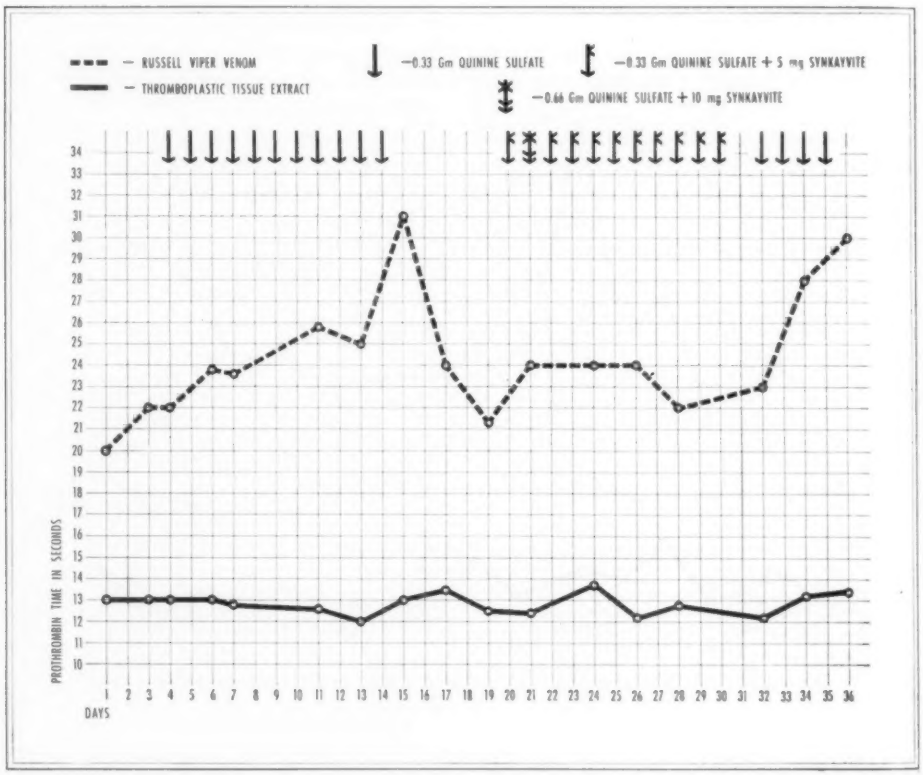
— RUSSELL VIPER VENOM
— THROMBOPLASTIC TISSUE EXTRACT
—0.33 Gm QUININE SULFATE
—0.33 Gm QUININE SULFATE + 5 mg SYNKAYVITE
—0.66 Gm QUININE SULFATE + 10 mg SYNKAYVITE
PROTHROMBIN TIME IN SECONDS
DAYS

CHART 2.—Effects of quinine sulfate and of quinine sulfate in conjunction with Synkayvite on prothrombin time values obtained with Russell viper venom and a fast-acting thromboplastic tissue extract in E. F., a white female, aged 35.

In order to elucidate the discrepancy between these findings and those of Quick, comparative prothrombin time estimations were carried out, employing viper venom on the one hand and a fast-

acting thromboplastic tissue extract on the other. With the former, prothrombinopenia was clearly demonstrable in 5 persons receiving quinine sulfate orally; however, with the latter it was not. The prolongations of the prothrombin time as reflected in the tests with viper venom were counteracted in these subjects if vitamin K was administered with the quinine.

We wish to express our appreciation to Dr. Harry Neivert, who made it possible for us to conduct this work in his laboratory and who exercised supervision over the test subjects. Also we wish to extend our thanks to Dr. Searle of Burroughs-Wellcome & Co., Inc., New York, who provided the "Stypven" Russell viper venom used for some of the prothrombin estimations.

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ELECTROCARDIOGRAPHIC OBSERVATIONS IN CHRONIC CHOLECYSTITIS BEFORE AND AFTER SURGERY

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It is well established that a relationship exists between gall bladder disease and coronary artery disease. As has been stated by Wolferth,[17] and shown in post-mortem studies by Walsh *et al.*[14] and Breyfogle,[4] the 2 conditions occur together more often than would be expected from the incidence of each alone. In clinical studies Willius and Fitzpatrick[16] and Schwarz and Herman[12] have noted a similar coincidence of cholecystitis and cardiac affections. The cardiac symptoms of 54% of the patients reported by Willius and Fitzpatrick improved following cholecystectomy. Straus and Hamburger[13] have described 2 cases with irregular cardiac rhythm that became regular after surgery. Improvement in cardiac symptoms after gall bladder surgery has also been noted by Babcock,[1] Graham and his associates[7] and Lichty.[8] Roberts[11] reported 5 cases diagnosed as angina pectoris because of typical histories. Subsequently each developed gall bladder colic and underwent cholecystectomy with complete relief of the anginal symptoms as well as the biliary colic. Miller[9] and Barker and his coworkers[2] have likewise noted that cardiac symptoms may mimic those of cholecystitis or *vice versa*.

Further indications of the relationship between the 2 conditions are the electrocardiographic abnormalities that not infrequently occur in cholecystitis either with or without cardiac symptoms and the frequency with which they revert toward normal following cholecystectomy, the most common abnormality being depression of the T waves. Fitz-Hugh and Wolferth,[6] in 1935, reported 6 cases with cardiac symptoms, T wave changes in the electrocardiogram and cholecystitis, all of which improved following cholecystectomy. Weiss and Hamilton[15] reported 21 patients with cholelithiasis, 4 of whom had abnormal preoperative electrocardiograms. Eight days after cholecystectomy, 3 of the tracings had returned to normal. Inasmuch as 1 of these patients had essential hypertension, the authors concluded that the gall bladder operation had caused improvement in only 2 of the 4 cases, both of those that showed improvement having inverted T waves preoperatively and upright ones 8 days later. Boas and Levy[3] and Clarke[5] each reported a case in which flattened T waves became upright after cholecystectomy. Moschcowitz[10] described a patient whose electrocardiogram showed a prolonged P–R interval preoperatively and a normal one after removal of a diseased gall bladder.

Although these authors have reported electrocardiographic changes, most of the literature has been concerned with clinical changes, and we therefore thought it worthwhile to review the electrocardiograms of the cholecystectomy cases done in this hospital during a 6 year period. The case that prompted us to do this is, I believe, of sufficient interest to warrant reporting it in some detail.

Case 1. A.M. (No. 1 in Table 1), a 60 year old man, was admitted to the University Hospital in April 1943, because of repeated attacks of severe epigastric pain, associated with abdominal distention and gaseous eructations relieved only by morphine. He also complained of chest pain that developed with exertion or mental perturbation and was relieved by nitroglycerin. Multiple gall stones were seen on radiographic films

TABLE 1.—DATA ON 18 CASES

Case No.	Sex/Age at operation	Cardiac symptoms	Preoperative observations: Electrocardiogram	Preoperative observations: Blood pressure	Operation	Postoperative observations: Electrocardiogram	Postoperative observations: Blood pressure
1	M/62	Angina, dyspnea; improved after oper.	5-25-45: diphasic T waves	140/85 (June '44)	Cholecystectomy, 6-1-45 (stones)	6-12-45: sl. flattening of T waves; impr.	150/85 (Jan. '46)
2	F/49	None	4-21-39: low T2	164/94 (April '39)	Cholecystectomy, 4-29-39 (stones)	1-12-46; neg.; impr.	152/92 (Jan. '46)
3	F/46	Sl. dyspnea for years; not changed by oper.	3-17-44: low T waves in I, II, CR_5 and CR_6	190/120 (Mar. '44)	Cholecystectomy, 3-21-44 (stones)	11-29-45: T waves larger; impr.	182/118 (Nov. '45)
4	F/46	Sl. dyspnea for 2 years; not changed by oper.	12-2-40: T3 abnorma	132/88 (Dec. '40)	Cholecystectomy, 12-3-40 (stones)	11-28-45: T waves larger; impr.	142/90 (Nov. '45)
5	F/51	None	8-10-43: small diphasic T waves	122/76 (Aug. '43)	Cholecystostomy, 8-18-43; cholecystectomy, 10-4-43 (stones)	11-29-45: T waves larger, not diphasic; impr.	114/70 (Nov. '45)
6	F/60	None	9-1-43: T waves abnormal	130/88 (Aug. '43)	Cholecystectomy, 9-5-43 (stones)	9-27-45: negative; impr.	114/80 (Sept. '45)
7	F/44	Dysp., dizziness for several years; not changed by oper.	3-21-44: T waves abnormal	190/100 (Dec. '43) 190/110 (Oct. '44)	Cholecystectomy, 12-9-43; choledochostomy, 10-20-44 (stones)	9-20-45: negative; impr.	210/120 (Sept. '45)
8	F/60	Occasional anginal attacks; none since oper.	4-10-45: small and sl. inverted T waves in I and CR_4; flat T waves in II	155/85 (April '45)	Cholecystectomy, 5-4-45 (stones)	8-22-45: sl. but definite impr. in T waves; impr.	160/100 (Aug. '45)
9	F/55	None	3-10-43: T wave changes	120/85 (Mar. '43)	Cholecystectomy, 3-11-43 (stones)	3-43, 8-43, 3-44, 12-44: sl. but definite impr. in T waves; impr.	140/80 (Mar. '44)
10	F/50	Mild dysp., palpit. and precord. pain; not related to exercise; not changed by oper.	8-27-40: slurred QRS complexes; diphasic T waves; raises question of myocard. infarction	160/100 (May '41)	Cholecystectomy, 5-12-41 (stones)	12-21-43: neg.; impr.; poss. due to healing of an infarct	140/90 (Dec. '43)
11	F/59	Angina, also generalized precordial pain not related to exercise; not changed by oper.	1935 and 1939: poss. old post. infarct; 1940 and 1945: no change	194/98 (Oct. '44)	Cholecystectomy, 5-45 (stones)	12-3-45: no change; unchanged	180/90 (Dec. '45)
12	F/74	Dysp. decompensation; not changed by oper.	3-23-43: auric. fibril., l. bundle branch block, and marked myocard. damage	185/120 (Mar. '43)	Cholecystectomy, 3-29-43 (stones)	7-43, 9-43, 9-44: no change; unchanged	150/70 (Sept. '44)
13	F/53	Weak. palpit.; not changed by oper.	1941, 1942, 1943: r. bundle branch defect	120/90 (1943)	Cholecystectomy, 2-14-44 (stones)	1944, 1945: no change; unchanged	125/85 (1946)
14	F/32	None	2-24-42: diphasic T waves	135/85 (Feb. '42)	Cholecystostomy, 3-3-42 (no stones)	11-16-44: no change; unchanged	152/96 (Nov. '44)
15	M/55	None	4-16-43: slurred QRS complexes; low T waves in I	116/75 (April '43)	Cholecystectomy, 4-21-43 (stones)	11-17-45: further change in T waves; worse	138/72 (Nov. '45)
16	F/47	Dysp., precord. pain; not related to exercise; not changed by oper.	1940, 1943: myocard. abnormality	138/90 (Feb. '43)	Cholecystectomy, 3-1-43 (stones)	9-1-43: further change in T waves; prob. other cardiac damage; worse	150/98 (1944)
17	F/59	Dysp., palpit.; cardiac failure in 1938 and 1939	10-7-38: myocard. damage	222/140 (Oct. '38)	Cholecystostomy, 12-9-38 (stones)	5-2-39: prob. ant. infarct; worse	200/110 (April '39)
18	F/57	Rheum. fever at 6 and 34; 3 anginal attacks per week before oper.; 1 per month after oper.	2-27-45: RST segment and T wave changes; digitalis effects	116/68 (Mar. '45)	Cholecystectomy, 3-28-45 (stones)	11-28-45: digitalis effects mask changes	150/82 (Nov. '45)

and an electrocardiogram showed T wave deformities and extrasystoles. Because of the obvious clinical and roentgenologic evidence of calculous cholecystitis, an operation was recommended. He preferred, however, to try conservative measures and cholecystectomy was not urged.

On a low fat diet he remained relatively free from gall bladder attacks although his angina continued. Late in 1943 he began to lose weight and an electrocardiogram in January 1944 still showed diphasic T waves in Leads I, II and CR_5 with a regular rhythm. With a slight increase in diet the episodes of colic increased in frequency and in April 1945 two attacks occurring within 2 days caused his readmission to the hospital. In view of his continued difficulty, surgery was deemed essential in spite of his cardiac symptoms and a cholecystectomy was done on June 1, 1945. The electrocardiogram taken 6 days prior to operation (Fig. 1*A*) showed less pronounced changes than any of the previous tracings but it was still definitely abnormal with diphasic T waves. Eleven days postoperatively this had improved so markedly that only slight flattening of the T waves could be seen (Fig. 1*B*). In the 10 months since June 1945, he has had no attacks of gall bladder colic and only 1 episode of anginal pain, occurring with the excitement of V–J Day. His electrocardiogram, the most recent being April 1946, has remained as it was in the immediate postoperative period; not normal but definitely better than any taken before operation.

In order to determine whether the improvement in this case was unusual, we reviewed the records of 621 unselected gall bladder operations performed in this hospital between September 1938 and December 1944. Only 66 of the patients had had an electrocardiogram within a year prior to operation, and 30 (45%) of these were negative. Of the 36 patients with abnormal electrocardiographic tracings, 17 could be followed. Five of the others had died and 14 could not be traced. The inclusion of the case (A. M.) previously reported in this paper makes a total of 18 patients to be considered. All had pre- and postoperative electrocardiograms and all but 1 had gall stones at operation.

Ten (56%) of that group (Nos. 1 to 10 of Table 1) showed marked improvement in the postoperative electrocardiogram. In No. 10, however, the preoperative abnormality may have been due to a myocardial infarct, the healing of which caused a return of the electrocardiogram to normal. The exclusion of this case, in which the relation to cholecystectomy may have been coincidental, gives 9 cases (50%) that showed electrocardiographic improvement postoperatively because of the surgical procedure. The postoperative tracings of 4 (22%) of the 18 were unchanged, 3 (16%) were worse and 1 (6%) could not be interpreted because of digitalis effects. None of these 10 patients, whose tracings reverted toward normal following surgery, had at any time electrocardiographic evidence of severe myocardial disease although 1 (No. 1) was nearly incapacitated by anginal attacks and another (No. 8) occasionally had such episodes. The first patient has had only 1 anginal attack since cholecystectomy and the other patient has had none.

Six patients (Nos. 11, 12, 13, 16, 17 and 18) had definite cardiac lesions as revealed by their electrocardiograms. After gall bladder operations, electrocardiographic evidence of the cardiac condition progressed in Cases 16 and 17, remained stationary in Cases 11, 12 and 13 and in Case 18 could not be interpreted because of digitalis effects. This latter patient, however, did have less anginal pain after operation.

If a systolic pressure over 170 and/or a diastolic pressure over 100 be regarded as constituting hypertension, then 5 of our patients were hypertensive. The electrocardiogram of 2 of these did not change postoperatively; 2 improved, and 1 became worse. It is possible that the T-wave abnormality noted in these patients was a transient change associated with their elevated blood pressure and that the improvement after surgery was coincidental. Eliminating Case 10 for the reasons already stated, and considering only the remaining 12 patients with nor-

mal blood pressure, 58% (7 cases) showed improvement in the postoperative electrocardiograms, (17%), 2 cases were unchanged, 17% (2 cases) became worse, and 8% (1 case) could not be interpreted because of digitalis effects.

Anginal symptoms were present in only 4 patients (Nos. 1, 8, 11 and 18). Following operation, the first of these improved markedly; 2 others (Nos. 8 and 18) had less frequent episodes; the fourth (No. 11) showed no change in the frequency or severity of her angina, which had always been mild.

To a certain extent the 18 patients reported here are a selected group because electrocardiograms undoubtedly were done only on those surgical patients with known or suspected cardiac disease. Therefore, the results cannot be strictly applied to all gall bladder cases. However, it is apparent that T wave changes in the electrocardiograms occur not infrequently with cholecystitis, either with or without cardiac symptoms, and, in a number of cases (50% in our series) revert toward normal postoperatively. The cause of the abnormal T waves is not known. At times they are part of a general picture suggestive of myocardial damage, in which case the need for surgery must be weighed against the cardiac status. However, deformed T waves in cases of cholecystitis do not always reflect heart disease. Possibly they are sometimes due to an abnormal concentration of some substance

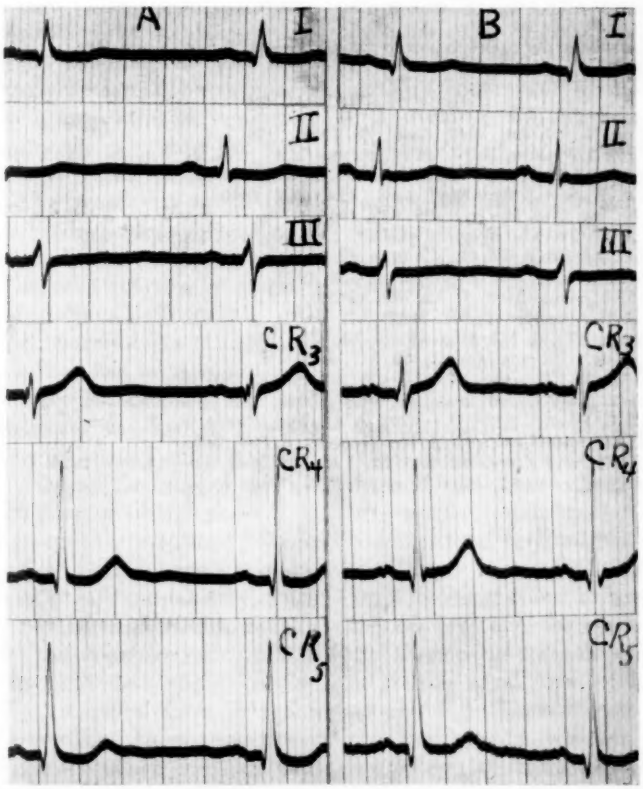

FIG. 1.—Case 1. Tracing A made 6 days before operation. Tracing B made 11 days after operation. The T waves in Leads I and II showed slight but definite changes toward normal and in Leads CR_4 and CR_5 became completely normal.

arising from perverted biliary tract function. In these cases with no definite cardiac damage, cholecystectomy may well improve the electrocardiogram as well as relieve the gall bladder symptoms and such patients should not be deprived of operation when it is indicated.

Conclusions. We have reported preoperative and postoperative electrocardiographic observations in 17 cases of calculous cholecystitis and in 1 case of noncalculous cholecystitis, all of whom had abnormal preoperative tracings. Including those with cardiac symptoms as well as those without, 50% showed reversion of the T waves toward normal following gall bladder surgery. Excluding the 5 patients with hypertension did not significantly change this percentage. In view of these results, T wave changes, unless associated with other indications of severe myocardial damage, should not be considered a contraindication to operation in chronic cholecystitis.

I wish to acknowledge my appreciation to Dr. Charles C. Wolferth and Dr. T. Grier Miller for their invaluable assistance.

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MONOPLEGIA FOLLOWING CAROTID SINUS PRESSURE IN THE AGED

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Since the publication of the classical contributions of Weiss and his co-workers on the clinical significance of hypersensitivity of the carotid sinus, the efforts of other investigators have established the frequency of this condition in older male individuals. Arteriosclerosis, hypertension and congestive heart failure are significant contributing factors, as is also the influence of drugs such as morphine and digitalis. Testing for sensitivity of the carotid sinus has become an important part of the physical examination in any person presenting attacks of syncope or atypical cardiac manifestations. That this procedure may have harmful effects and cause permanent damage has been revealed in several recent publications. To add another example of irreversible cerebral damage following carotid sinus pressure and to discuss the implications of this experience is the purpose of this paper.

Weiss and Baker[17] distinguished 3 forms of reflex response to carotid sinus stimulation: the vagal or cardio-inhibitory, characterized by marked bradycardia, usually with asystole; the depressor, with fall in blood pressure and but slight cardiac slowing; and the cerebral form in which syncopal or convulsive phenomena occur without significant change in heart rate or blood pressure. Mixed forms were recognized and in later papers[4,18] they were able to separate the cerebral type more completely with the use of atropine to block the vagal response. In these later studies they also demonstrated that simple occlusion of the carotid artery well below the sinus did not elicit the cerebral reactions. They attributed the cerebral response to localized vasoconstriction in reaction to the impulses arising in the carotid sinus. However, they were unable to find any evidence of diminution of total cerebral blood flow or of cerebral anoxia, such as clearly occurred in the course of the cerebral reactions secondary to the asystolic type. Further evidence against the vasoconstrictor hypothesis was the inability to prevent or modify the cerebral response by the administration of vasodilators, or by inhalation of oxygen. On the other hand, the spinal fluid dynamics observed in the course of the reactions suggested that variations of blood-vessel caliber did occur in the cerebral circulation. Lennox, Gibbs and Gibbs[8] likewise failed to find any evidence of cerebral anoxia and they attributed the unconsciousness and other direct cerebral phenomena to a purely neural inhibition which they likened to catalepsy and to reflex epilepsy. However, most observers appear to hold to the idea of a local cerebro-vascular response not extensive enough to affect total cerebral blood flow or oxygenation. Numerous electro-encephalographic observations have been made on the cerebral type of carotid sinus reflex and there exists some difference of opinion as to the usual form of brain wave response.[5,10,14] These studies do not clarify the problem of whether the effect is secondary to circulatory reaction or is primarily neurogenic.

It should be noted that the cerebral phenomena usually observed in the central type of carotid sinus reflex are reversible in character, consisting chiefly of transient unconsciousness or syncope, convulsive movements, or numbness and paresthesias generally referred to the contralateral side of the body. That an irreversible, permanent cerebral effect of carotid sinus stimulation might occur was first suggested by Galdston, Govons, Wor-

tis, Steele and Taylor.[6] They noted a possible causal relationship between a hyperactive carotid sinus of the vagus type and contralateral complete thrombosis of the common, internal and external carotid arteries with hemiplegia. More direct, and even dramatic, confirmation of this hypothesis was the report of Marmor and Sapirstein[11] on the occurrence of a fatally progressive thrombosis of both anterior cerebral arteries following stimulation of the right carotid sinus in a man of 53 years. In this case there was slowing of the pulse without asystole, and clonic twitchings with syncope from which the patient quickly recovered, only to lapse within a few minutes into stupor, with incontinence and a right hemiplegia. Thrombosis of the left anterior cerebral artery was diagnosed. Later the paralysis involved the opposite side as well. At postmortem, recent thrombus formation was found in both anterior cerebral arteries. In this case, too, the thrombotic process in the cerebrum occurred primarily on the side opposite to that of the stimulated sinus and appears to have been induced in the course of the diminished blood flow secondary to the cardio-inhibitory type of carotid sinus reflex. Whether there was an element of the cerebral form of reflex response as well is speculative.

During the 5 year interval since the case report of Marmor and Sapirstein, the sole reference to permanent cerebral effects as a result of carotid sinus pressure is to be found in Levine's textbook, "Clinical Heart Disease."[9] In his discussion of the treatment of paroxysmal auricular tachycardia he notes the occurrence of hemiplegia as a hazard of carotid sinus stimulation in the aged.

The most significant and arresting observations are contained in a recent paper by Askey on hemiplegia following carotid sinus stimulation.[1] As a result of the pooled experience of the California Heart Association, 7 such occurrences are described. This investigator is of the opinion that a direct cerebral reflex occurs with resulting vasoconstriction. In the elderly and particularly in the presence of cerebral arteriosclerosis this usually reversible phenomenon precipitates a chain of events which leads to occlusion of the vessel by a thrombotic process. In all 7 cases the cerebral hemisphere involved was on the same side as the carotid sinus stimulated. In 2 instances either slight or no cardiac slowing occurred and in these cases at least the hemiplegia could not be explained as due to diminution in total cerebral blood flow secondary to asystole. This point of view is strengthened by the history of recurrent transient hemiplegia in 1 of these patients. This history, together with the evident presence of a hyperactive sinus in all these cases, also argues strongly against the idea that simple carotid artery occlusion was responsible for the cerebro-vascular thrombosis. Hemiplegia occurred on only light massage of the sinus without the possibility of occlusion of the vessel during testing.

These observations indicate that in some of these cases, if not in all, the paralysis represented an irreversible reaction to the cerebral type of carotid sinus hypersensitivity. Askey cites Weiss and his co-workers' earlier observation on the reversible forms in excluding the possibility that simple temporary closure of the carotid might induce the cerebral thrombosis.

However, it must be granted that, although the mechanism most probably depends on the sinus reflex, it may not be so mediated in every instance. Particularly in the aged, obstruction to carotid blood flow may be poorly borne. Ray and Stewart[13] cite an instance of arteriovenous fistula between the internal carotid artery and the cavernous sinus in a man of 61 years. Pressure on the carotid sinus on the same side induced convulsions and unconsciousness. Procainization of the sinus did not abolish this response, which they then attributed to simple closure of the carotid by pressure. Engel, in discussing the general aspects of syncope, has pointed out that the clinical picture may be modified by preëxistent

structural defects, such as cerebral arteriosclerosis, and that elderly patients may be expected to lose consciousness more quickly and to recover more slowly.[2]

Previous investigators[7,16,17] have indicated that hypersensitivity of the carotid sinus mechanism and the clinical syndromes resulting from it occur frequently in old age. A study of the responses to carotid sinus stimulation was undertaken among residents of a home for the aged. One hundred and eighty-eight persons were tested, 106 female and 82 male, with an age range from 62 to 92 years, 22 (12%) showed a response with cardiac asystole. There were 2 instances of the reversible form of cerebral response. In accordance with the warnings of various observers, all patients were tested in the recumbent position. Nonetheless the last subject in the series developed a monoplegia within a few minutes following carotid sinus testing.

Case Report. The patient, a man of 83 years, had suffered from hypertension for many years. The past history was unrelated to the present illness except that he had an old Bell's palsy with residual right facial weakness. The family history was of interest in that the patient's mother had died at 94 years and his father at 79 years of age. At the time of admission to the home, 3 years before the present incident, his blood pressure had been found to be 230/100. Otherwise the physical examination revealed only moderate cardiac enlargement, the chest Roentgen ray showed the heart to be somewhat globular in shape but not definitely enlarged and the aorta elongated. Hemoglobin was 81%; red blood cells, 4,100,000; white blood cells, 5600 (polymorphonuclears, 67%; lymphocytes, 29%; monocytes, 3%; eosinophils, 1%). The blood Wassermann reaction was negative. The urine showed many white blood cells, clumped, and a trace of albumin. Blood glucose was 90 mg. per 100 cc., and the urea nitrogen 13 mg. Subsequent blood pressures ranged from 185/90 to 240/100. On several occasions he had episodes of wheezing dyspnea, usually considered bronchial rather than cardiac in origin. He was placed on digitalis for a short while but was not taking this, or any other medication, at the time of his carotid sinus test. Electrocardiograms taken over a 3 year period showed chiefly left axis deviation and high voltage of complexes indicative of left ventricular hypertrophy. There was also semi-inversion of T–1 and T–2. The tracings were essentially unchanged over this time.

This individual was included in the group for routine testing of carotid sinus responsiveness. As with the others, he was tested while lying in the supine position on an examining table. Pressure was made first on the right and then on the left carotid sinus area, each side for 15 seconds. There was no response in terms of cardiac slowing or asystole and no noticeable change in heart sounds. No evidence of cerebral response was observed in that there was no syncope, no convulsive phenomena of any kind, no fixation of gaze and no facial pallor as has been so often observed to accompany the cerebral form of response. Almost immediately after this negative test he was allowed to rise from the examining table, and left the room without any assistance. However, within a few minutes our attention was called to him by other residents of of the home and he was found nearby, sitting in a chair complaining that his right arm felt heavy. On examination he was unable to raise the right upper extremity, which was in a state of flaccid paralysis. He was placed at bed rest and given vasodilator medication. In the next day or 2 he developed slight drowsiness and dysarthria which rapidly cleared. There was no evidence of involvement of the right lower extremity and no pathologic reflexes were observed. Within several days he was sitting up and not long after he was up and about.

His monoplegia has persisted and he finds it necessary to keep his arm in a sling for comfort. Over a year has passed since the incident, and paresis of the arm still persists. No further cerebral manifestations have been noted.

The experience here recorded, supported as it now is by the observations of others, is evidently not an isolated one. Carotid sinus stimulation can no longer be regarded as an innocuous procedure in the aged or in any patient with evidence of arteriosclerosis or with long-standing hy-

pertension. We are aware that the complications to which we draw attention must be rare. Sigler tested 1886 individuals without any untoward incident.[16] Engel, who has had an extensive experience with carotid sinus stimulation, states: "I am not familiar in my personal experience with any instance of untoward cerebrovascular complication following carotid sinus testing."[3]

Despite the rarity of this irreversible reaction, its serious and permanent nature impels us to warn against the casual employment of this test. Others have advised that the test be performed "cautiously" and have recommended that the subject be in the recumbent position. As to the first, it should be pointed out that the reflex mechanism once set in motion cannot be controlled. The sinus is either stimulated or not, but it is impossible to do it cautiously. Our own case demonstrates that the recumbent position will not prevent these unfortunate accidents. This precaution may be helpful in cases of the vagal type by avoidance of syncope and disturbance of cerebral blood flow secondary to asystole but it will not have any effect where the efferent impulse affects the cerebrum or its vessels directly.

Our conclusion must be that the test should be reserved for those cases where it will serve a diagnostic or therapeutic purpose of definite importance. It should not be used as a routine test in patients past 50 years of age. It should not be employed in the elderly to stop attacks of supraventricular tachycardia except in the unusual and obstinate cases where other measures have failed.

An interesting speculation which naturally stems from these observations pertains to the possible rôle of the hypersensitive carotid sinus mechanism in the spontaneous precipitation of cerebral accidents. The cases of Marmor and Sapirstein, and of Askey, and the present instance show that cerebro-vascular thrombosis may occur in response to stimulation of the carotid sinus, whether the hypersensitive mechanism is of the vagal or the cerebral type. In either case the abnormal arteriosclerotic cerebro-vascular apparatus permits thrombosis when there is a significant disturbance of blood flow, probably together with vasoconstriction.

Recognition of this pathogenetic mechanism as of possible significance in the causation of cerebral accidents suggests the possibility of instituting prophylactic measures in suitable cases. Thus in the elderly, and indeed in all those past 50 years, where hypertension or arteriosclerosis is present, whether cerebral, coronary or peripheral, avoidance of all constriction of the neck should be advised. These patients should be warned against abrupt and violent movements of the neck or head, and against straining at stool or heavy lifting and bending.

Furthermore, consideration should be given to the avoidance of cholinergic drugs such as neostigmin, and particularly morphine and related medications. These agents certainly potentiate the vagal form of the hypersensitive carotid sinus reflex, if not the cerebral. The authors have had an opportunity to observe that carotid sinus pressure often brings a paroxysm of auricular tachycardia to a stop after the administration of morphine, although it was previously ineffective. Digitalis has been found to sensitize the vagal type of reflex[4,12] and Weiss and co-workers suggest that it may have a similar action in the cerebral form.[4] We join these authors in warning against unnecessary digitalization as increasing the risk of cerebral complications in the elderly. Weiss and coworkers particularly deplored the routine preoperative use of digitalis in such patients. Rovenstine and Cullen[15] likewise noted the dangers in preoperative use of digitalis or morphine in patients with a hypersensitive carotid sinus, and advised that during the operation, and in the administration of anesthesia, too vigorous manipulation of the head and neck be avoided. In the elderly morphine should be avoided, preoperatively and otherwise, and if used, should always be accompanied by atropine sulfate, $\frac{1}{100}$ gr. It is possible

that atropine should be more widely used in the aged to block the vagal type of hyperactive carotid reflex. It might be included, with benefit, in the commonly used vasodilator combination of theophylline, papaverine and phenobarbital, in the management of patients with arteriosclerosis either with or without hypertension.

Summary. A man, aged 83 years, with long-standing hypertension, developed a permanent right monoplegia within a few minutes after carotid sinus testing. The literature is reviewed with particular reference to the occurrence of cerebrovascular complications following carotid sinus stimulation. A warning is sounded against the casual employment of carotid sinus pressure either as a diagnostic test or therapeutic measure in aged patients suffering from hypertension and arteriosclerosis. The possible rôle of the hypersensitive carotid sinus reflex in the precipitation of spontaneous cerebral accidents is discussed. On the basis of this hypothesis, suggestions for the prophylaxis of cerebro-vascular accidents in the aged are outlined.

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TREATMENT OF CARRIERS OF ENDAMŒBA HISTOLYTICA AND OTHER PROTOZOA WITH CARBARSONE, CHINIOFON AND VIOFORM

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Frequency of the Carrier State: In a previous publication Wenrich, Stabler and Arnett[3] found that 4.1% of 1060 students entering a Philadelphia college were symptomless carriers of *E. histolytica*. A later study[4] revealed an incidence of 11.1% of carriers among 190 food handlers of this institution. A survey of a home for the aged on the outskirts of Philadelphia[5] revealed an incidence of 11.3% of carriers among 53 inmates and employees. These figures are not to be interpreted as indicating an undue prevalence of *E. histolytica* in the institutions in question or in the city of Philadelphia, but merely as confirming for this locality the opinion of Craig[2] and others, that 5 to 10% of the population of the United States harbor *E. histolytica* in their intestinal tracts. Other protozoa were, of course, encountered commonly: interest, however, centered around *E. histolytica* because of its potentialities for producing amebic dysentery. It should be emphasized, however, that the work herewith reported applies only to carriers, and not to patients with amebic dysentery. The treatment of the latter disease offers a different, and more difficult problem which will not be dealt with here.

Method and Object of Study. Although we found no evidence that the presence of *E. histolytica* in the stools of our subjects did them any harm, however, it was felt advisable to relieve them of their parasites. To accomplish this, 2 courses of chiniofon or carbarsone were administered to alternate cases during the early part of this study. Later only 1 course was given, and, finally, vioform was given to 12 successive cases. Repeated stool examinations for all protozoa were made before, during and after treatment. Where possible reëxaminations were also made at intervals after the treatment had been stopped.

Feces samples, obtained without laxatives, were examined by D. H. Wenrich, Ph.D., and R. M. Stabler, Ph.D., of the Zoölogy Department of the University of Pennsylvania, both as wet preparations and after fixing and staining in the manner referred to in a previous article.[1] The following criteria and terms were adopted: (*a*) For inclusion in this study, at least 2 positive stools before treatment. (*b*) For "disappearance," consistently negative stools (at least 2) during treatment or for 1 week thereafter. (*c*) The term "reappearance" is used to denote the recurrence of 1 or more positive stools after the "disappearance" of the organism has occurred (*d*). When stool samples were submitted irregularly during the course of treatment, the time of disappearance was assumed to have occurred on the 1st day after the last positive stool.

The dosage of carbarsone was 1 capsule of 0.25 gm. given with breakfast and 1 with supper for 10 days. That of vioform was 1 capsule of 0.25 gm. 3 times daily for 1 week. That of chiniofon was 1 pill of 0.25 gm. 3 times daily after meals on the 1st day, 2 pills after meals on the 2nd day to the 5th, and 3 pills after meals on the 6th and 7th days. When diarrhea or other unpleasant symptoms arose, medication was temporarily discontinued, to be resumed later with the same, or another drug, depending upon circumstances.

Results. *E. Histolytica.* Sixteen *E. histolytica* carriers treated with chiniofon fulfilled the criteria for inclusion in this study. In 4 of these the drug was stopped because of diarrhea. Four other cases complained of lesser degrees of diarrhea not requiring the discontinuance of the drug and the remaining 8 had no symptoms. In 11 of the 12 cases continuing treatment, *E. histolytica* disappeared from the stools in an average of 2.9 days. The 12th case revealed *E. histolytica* 6 days

after the cessation of the first course of treatment, but the organisms disappeared on the 4th day of the second course of chiniofon.

Thirteen persons receiving carbarsone fulfilled the requirements for inclusion. Of these, 1 complained of diarrhea, 1 of diarrhea and dizziness, 1 of constipation and 1 of itching within the rectum. In 1 case the symptoms were sufficiently severe to require temporary discontinuance of the drug. *E. histolytica* disappeared from the stools in 12 cases, the average time required being 1.9 days. In the 13th case *E. histolytica* was found in 3 of 4 specimens submitted before carbarsone was given. Three stools submitted during the first course of carbarsone were negative. After a 10 day rest period during which no stools were submitted, a second course of carbarsone was given and on the 5th day of this course a stool was positive; 42 days later a final sample was submitted which was negative.

Twelve individuals receiving vioform fulfilled the requirements for inclusion. Of these, 1 complained of diarrhea. Here medication would have been changed to another preparation had not the organism disappeared from the stools and no further treatment was deemed necessary. In all cases treatment was successful, the average time required for the disappearance of *E. histolytica* from the stools being 1.7 days.

Other Organisms. Although the presence of protozoa other than *E. histolytica* was not regarded as an indication for treatment, yet while treatment was being administered to the *E. histolytica* carriers, it seemed worth while to record its effects on any other protozoa which happened to be present.

E. coli: Of 4 carriers of *E. coli* the organisms disappeared during chiniofon medication in 3 instances in an average of 3.7 days, but reappeared in 1 of the 3. Of the 6 carriers of *E. coli* receiving carbarsone the organisms disappeared from the stools in all cases in an average of 3.1 days but reappeared in 2 instances. There were no carriers of *E. coli* in the vioform treated group.

Endolimax nana: This organism was present in 5 individuals in the group treated with chiniofon, but in only 2 of them did the organisms disappear from the stools, the average time being 6 days. In 1 of these endolimax reappeared after treatment was stopped. In the carbarsone treated group 7 revealed endolimax which disappeared from the stools in all cases in an average of 2.9 days, but reappeared in 2 cases. In 5 of the vioform treated group endolimax disappeared from the stools in an average of 1 day, but all reappeared after treatment had been stopped.

Diendamœba fragilis was present in 2 of the chiniofon treated group, disappeared in an average of 4 days and reappeared in 1 instance. It was present in neither the carbarsone nor vioform treated groups.

Iodameba was present in the carbarsone treated group only, occurred but once, and disappeared in 3 days without reappearing.

Giardia was present in 2 of the chiniofon treated cases, and disappeared 5 days after treatment was begun in 1 of these. The other case did not become negative on 15 tablets (3.7 gm.) of chiniofon; this drug was discontinued because of the appearance of diarrhea. A subsequent course of carbarsone resulted in the disappearance of giardia without recurrence.

Chilomastix: Of 2 instances of chilomastix infestation the organism disappeared on the 2nd day after the administration of vioform was begun in 1 instance, but later reappeared. In the 2nd instance the organism disappeared 3 days after the administration of carbarsone, the data being insufficient to indicate whether or not there was any reappearance.

Summary. 1. Chiniofon, carbarsone and vioform all proved efficient in ridding apparently healthy carriers of *E. histolytica*.

2. These drugs did not prove as efficient in eliminating other protozoa from the stools.

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THE PRESENT STATUS OF TRYPARSAMIDE IN SYPHILOTHERAPY

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In evaluating any drug, 2 primary questions arise: (1) the toxicity of the agent; and (2) its therapeutic efficacy. An additional problem in pharmacotherapeutics is the comparison of the drug under consideration with other agents in terms of toxicity and efficacy.

Tryparsamide, a pentavalent arsenical, was synthesized by Jacobs and Heidelberger in 1919.[12] Pearce and Brown[23] observed that it had very little effect on the spirochetes in the lesions of experimental rabbit syphilis. Moore and his associates[20] were unable to influence the course of infectious syphilis in patients. There was no regression of the skin manifestations of 6 patients with infectious syphilis, and in 3 the *T. pallidum* was demonstrable on repeated dark-field examinations. Dubois[6] followed a patient who developed a chancre while receiving weekly injections of tryparsamide for chronic trypanosomiasis. The spirochetes flourished during the arsenotherapy and the drug had no apparent effect on the course of the syphilis. The inability of tryparsamide to influence either the spirochetes or lesions of infectious syphilis is apparent from these few observations.

Pharmacology. The assumption is well supported that organic arsenicals are therapeutically active by virtue of their ability to inhibit essential metabolic processes of the parasite. Voegtlin, Dyer and Leonard[33] and later Rosenthal[26] suggested that trivalent arsenicals unite with the cytoplasmic sulfhydryl (SH) groups of the organism. These workers presented evidence that the activity of the pentavalent group depends on the ability of the tissues to reduce the drugs of higher valency to the trivalent form. Recently Hogan and Eagle[11] have suggested that the therapeutic value of an arsenical compound is proportional to the amount clinically bound by the pathogen. It was found that trivalent arsenicals are bound by tissues to a greater degree than are the pentavalent compounds. The amount of arsenical remaining in the tissues after injection of 700 mg. of tryparsamide was of the same order of magnitude as after injection of 0.8 mg. of phenyl arsenoxide (trivalent arsenical). This suggests that

the affinity for animal tissues is 900 times greater for arsenoxide than for tryparsamide.

Lorenz[17] found that between 80 and 90% of tryparsamide is excreted within 1 day following intravenous injection. Young and Muehlberger[39] noted that between 88 and 95% of tryparsamide is excreted in the urine within 24 hours and much of the drug is recovered *unchanged*. In contrast, Voegtlin and Thompson[34] recorded that arsenoxide is tenaciously retained in the body cell. These observations confirmed the analysis of Young and Hamilton[38] who found that much of tryparsamide is excreted in the urine as such within 6 hours of an intravenous injection. Hogan and Eagle showed that arsenicals poorly bound by tissues (as tryparsamide) are rapidly excreted, whereas those compounds firmly held in the tissues (as trivalent arsenicals) were excreted at a correspondingly slower rate. In the case of tryparsamide 40% is eliminated from the body within 1 hour. These observations make it apparent that there is little opportunity for the pentavalent arsenicals to be utilized therapeutically.

In spite of the obviously low treponemicidal effect of tryparsamide, it has been postulated that the drug hastens recovery in neurosyphilis because of a greater penetrability of the central nervous system. This concept is based primarily on the work of Voegtlin, Smith, Dyer and Thompson,[32] who injected trypanosomes into the subarachnoid space of rabbits. Subsequently, various arsenicals, including tryparsamide, were administered intravenously, and 24 hours later the subarachnoid fluid was examined for trypanosomes. It was found that tryparsamide had the greatest trypanocidal effect, and sulfarsphenamine was almost as effective. This was interpreted as evidence of greater permeability of the meninges by the pentavalent drug. These experiments of Voegtlin and his associates have been accepted as evidence for the superiority of tryparsamide over the trivalent arsenicals for treatment of neurosyphilis. The greater vulnerability of the trypanosomes to tryparsamide as a specific agent has not been taken into consideration, nor has any effect been made to differentiate between penetration of the meninges and penetration of the nervous tissue.

Cornwall and his associates[3] found that less arsenic may be recovered from the spinal fluid following an injection of tryparsamide than after arsphenamine, neoarsphenamine or silver arsphenamine. In fact, for comparable amounts, 24 times more arsenic was obtained from the spinal fluid after an injection of silver arsphenamine than after tryparsamide. Fordyce and Myers[9] observed that the brains of mice contained 9 times more arsenic after an injection of silver arsphenamine than after tryparsamide, although the amount of silver arsphenamine, a trivalent arsenical, was only one-fifteenth the amount of the pentavalent material. The workers concluded that "tryparsamide does not possess an unusual power of arsenic penetration into the central nervous system. Therapeutic penetration is hypothetical in that other factors which may enter into this condition are not available either experimentally or clinically." Von Kennell and Kimmig[35] were unable to recover any arsenic from the spinal fluid of patients treated with solvarsin, a pentavalent arsenical similar to tryparsamide.

From the experimental data, there is little satisfactory evidence that tryparsamide possesses either greater penetrability or affinity for the central nervous system than the trivalent arsenicals. When the clinical observation, that tryparsamide is unable to influence either the lesions or spirochetes in infectious syphilis, is added to the pharmacologic material cited, one would not anticipate that the drug will be a powerful agent for the treatment of neurosyphilis.

Toxicity. Following the introduction of tryparsamide, relatively few constitutional reactions were reported. Nitritoid crises and gastro-intestinal complaints were virtually unknown. Kopp and Solomon,[13]

in a review of their cases, found a definite increase in reactions from 1923 to 1939. In more recent years, 8.6% of the patients experienced nitritoid crises, whereas from 1923 to 1937 these reactions were less than 3%. Gastro-intestinal symptoms increased from approximately 1 to 7.1%. These workers also noted skin lesions, often of an urticarial nature, chills and fever drowsiness, tremors, emotional upset, dizziness, headaches and, more rarely, transient peripheral nerve damage, visual and auditory hallucinations, convulsions and coma. These complications often did not appear until after extensive treatment. Traenkle and Dulce[30] described liver necrosis in 2 patients after tryparsamide therapy. Because nitritoid crises were considered so rare in 1938, case reports were made by Astrachan and Franks,[1] Cormia,[2] and Levy.[16] Downs and his associates[5] found that 13.5% of their patients developed nitritoid crises after tryparsamide, and a smaller group developed gastro-intestinal complaints. Moore[19] recorded a definite increase in toxic manifestations and suggested the possibility that impurities in recent manufacture might be responsible.

Optic nerve damage was observed by the first clinicians to use tryparsamide therapeutically. Pearce[22] treated 77 patients for trypanosomiasis and found 17 instances of visual complaint. Ten recovered completely, but in 7 permanent nerve destruction occurred. Lorenz and his associates[18] found that 40% of their patients developed evidence of toxic amblyopia as a dosage of 5 gm. of tryparsamide weekly. Woods and Moore[37] followed 241 patients treated once weekly with 3 gm. of the drug, and observed that 94% of reactions occurred between the first and tenth intravenous injection. Of the entire group, of patients, 5.5% developed objective evidence of damage to the optic nerve, and an additional 10% complained of visual disturbances. Patients with tabes dorsalis and general paresis were especially prone to develop restricted visual fields. This was observed in 23% of the patients with these serious manifestations of syphilis, whereas in patients without evidence of neurosyphilis, damage was detected in 6.2%.

Sloan and Woods[27] studied this problem and found 5.3% of 2087 patients experienced subjective symptoms after tryparsamide treatment. These complaints were "dazzling, shimmering or a glare as produced by bright light on snow." These symptoms usually began after several injections of the drug, but occasionally began after the first few treatments. The subjective complaints were often transient, lasting from a few hours to a few weeks. Of the group of 2087 patients, 71 (3.4%) subsequently showed objective evidence of permanent optic nerve damage consisting of constriction of the visual fields. Powell and Smith[24] studied 16 patients for detailed changes following tryparsamide therapy. Visual fields were done prior to each injection, and it was found that 11 of the 16 patients developed definite constrictions of the peripheral fields between the third and eleventh treatment. None of the patients had any evidence of optic nerve damage prior to the institution of therapy.

Kopp and Solomon[13] noted that the type of syphilitic lesions may bear some relationship to susceptibility to visual disturbance. In their series, 24% of the paretic group and 43% of the tabetic group developed eye complications, but none of the patients with meningovascular syphilis were handicapped.

Therapeutic Efficacy of Tryparsamide. The first report on the use of tryparsamide was made by Lorenz and his associates[18] in 1923. They found that 7 of 12 cases of early paresis and 21 of 42 cases with advanced paresis improved greatly and were able to return to work. However, some of the cases relapsed, and it was found that recovery was not permanent unless mercury was added as a therapeutic agent. This is both the first and the most enthusiastic report in the literature. The following year, Moore, Robinson and Keidel[20] described their results in 27 cases

of paresis, in 6 patients with tabes, and in 8 patients with asymptomatic neurosyphilis. This series differs appreciably in 2 important respects from that reported by Lorenz. Only 2 of the 40 cases, including the paretics, were sufficiently ill to require hospitalization. Also, the authors write that "secondly, 32 of the 40 cases had already been subjected to prolonged and intensive antisyphilitic treatment, sometimes with intraspinal therapy, though symptoms and physical signs had often already disappeared before tryparsamide was begun." However, the authors go on to say, "In spite of these differences in material and procedure, our results are in essential agreement with those of Lorenz and his co-workers." Four patients in the series with negative serologic tests for syphilis developed positive reactions while undergoing tryparsamide therapy.

In 1924, Moore and his associates[21] again reported favorably on the efficacy of tryparsamide, considering it of particular value in general paresis, meningovascular syphilis and the majority of cases with tabes dorsalis. Solomon and Viets[29] reported that tryparsamide was approximately as valuable as trivalent arsenicals in treatment of meningovascular syphilis, of little benefit in tabes dorsalis, and helped a small number of cases with general paresis.

When Lorenz reviewed his earlier work in 1928, he found that the therapeutic results were satisfactory after 5 years in 87% of the cases of neurosyphilis, when mercury had been added to the tryparsamide therapy. No reference is made to symptomatic and asymptomatic cases. Reese,[25] in 1933, reviewed the earlier work done by Lorenz and his associates. He reported that tryparsamide must be used over a period of years to be effective. Reese added, "At the onset we used tryparsamide without any antisyphilitic medication, but the noted beneficial effect on the clinical and serologic picture remained stationary, especially with regard to the clinical improvement. The addition of mercury resulted in more permanent improvement of the serologic findings, as well as a more rapid prolonged clinical benefit." The Wisconsin group claimed clinical arrest or remission in 54% of general paresis and 78% of the meningovascular syphilis. Patients with tabes dorsalis with lancinating pains, urinary disturbances and impotency were often relieved. Ebaugh and Dixon[7] reported that among 52 paretics marked improvement was obtained in 15 cases. Wile and Wieder[36] reported on a group of patients treated with tryparsamide. They found improvement in cells and protein of the cerebrospinal fluid, but little change in the colloidal gold or Wassermann reaction. They noted clinical improvement in but 7 of 32 paretics, 2 of 7 tabetics, and 2 of 12 taboparetics. From these data they assumed that tryparsamide could be expected to be of value in one-third of the patients with neurosyphilis.

Solomon and Epstein[28] reported on 81 patients with general paresis and found that they could arrest the deterioration in 42%, and that in the remaining 58% the process was uninfluenced. The spinal fluid became normal in 26.7% between 1 and 9 years after tryparsamide therapy was begun. Seventeen patients who failed to respond to tryparsamide obtained striking benefits from malaria. The authors concluded that "the clinical results of treatment with tryparsamide do not differ greatly from those obtained by malarial therapy." Because general paresis is invariably a fatal disease, these reports cannot be discounted.

Hinrichsen[10] reviewed the results of many writers and learned that, although as high as 50% remissions were reported with early paresis, only 22.5% of advanced cases improved. Since the results in the advanced cases varied from zero to 80%, these figures must necessarily be viewed with skepticism.

Lees[15] described excellent results in tabes dorsalis in 200 patients who received 2 years of combined tryparsamide and bismuth therapy. He noted reduction in sensory disturbances in 78%, diminution

of ataxia in 65%, and alleviation of bladder difficulties and gastric crises in an undisclosed number. Dattner[4] finds his own experiences at great variance from those of Lees, and believes tryparsamide of little value in eliminating tabetic symptoms. In the review by Hinrichsen, various authors claim improvement in 20 to 75% of patients with symptoms of tabes dorsalis.

Clinical Study. There are registered in the Syphilis Clinic of the New York Hospital 736 patients with asymptomatic neurosyphilis and 355 patients with tabes dorsalis. All of these cases have been reviewed in an effort to evaluate the toxicity and therapeutic efficacy of tryparsamide.

Toxicity. Study of the group with asymptomatic neurosyphilis revealed that 206 patients were followed an average period of 6.1 years, and at least 2 specimens of cerebrospinal fluid were obtained 1 or more years apart. Of this group of 206 asymptomatic patients, 139 received tryparsamide at some time during their course of antisyphilitic treatment. Sixty patients (43%) developed toxic reaction of such a degree that tryparsamide injections had to be discontinued. There were 15 instances of minor reactions, including 11 cases of nitritoid crisis and 4 patients who experienced gastro-intestinal upsets, characterized by nausea and vomiting.

It has been customary in this clinic to obtain an ophthalmologic consultation prior to the initiation of tryparsamide therapy. This examination routinely includes examination of the optic nerve, determination of corrected visual acuity and plotting of peripheral fields. If a patient complained of subjective evidence of toxicity, as photophobia, glaring or "fuzzy" vision, treatment was interrupted until the patient could be reëvaluated by the ophthalmologist. Patients who were reported as showing pallor of the disk or decrease in visual fields or optic nerve damage due to any cause as severe glaucoma or retrobulbar neuritis were not permitted to have tryparsamide again. In spite of these detailed precautions, 45 patients of the 139 who received tryparsamide (32%) developed subjective evidence of optic nerve sensitivity to the pentavalent drug, and subsequent studies showed that in 17 instances there was definite and permanent visual damage. These 17 patients with permanent visual damage represent 12% of all patients with asymptomatic neurosyphilis who receive one or more injections of tryparsamide.

Of the 355 patients with tabes dorsalis, 202 were suitable for study. This group was followed for an average of 5.8 years, and, of these, 126 received tryparsamide at some period during their course of antisyphilitic treatment. There were 22 instances of minor reactions, including 10 examples of nitritoid crises, 5 patients who had gastro-intestinal upsets, and 4 patients with dermatitis, plus 3 who experienced other minor disturbances; 47% of the tabetic group (59 of 126) who received tryparsamide developed subjective symptoms of injury to the optic nerve. Subsequent evaluation of these 59 patients revealed that 27 progressed to objective evidence of optic atrophy with some pallor of the disks and reduction in the peripheral visual fields; 27 patients recovered entirely, but the fate of 5 cannot be determined because of their failure to return to the clinic. It is apparent, then, that of the 126 tabetics who were exposed to tryparsamide therapy, at least 21% (27 of 126 patients) developed impaired vision. The toxicity of tryparsamide in patients with asymptomatic neurosyphilis and in tabes dorsalis is summarized in Table 1. No effort was made to evaluate the damage done in general paresis, because often these patients, in the presence of the psychosis, are unable to protest minor visual changes before excessive harm has been done.

Inefficacy of Tryparsamide. In the present study, only patients with asymptomatic neurosyphilis and tabes dorsalis are considered. Evaluation of patients with meningovascular syphilis is difficult because the group is heterogeneous and

patients often improve spontaneously. Almost every patient with general paresis in the New York Hospital Clinic received either malaria or penicillin therapy, and consequently this group is not studied.

In spite of the frequency of overlapping treatment schedules which include trivalent arsenicals as well as bismuth in the present series of patients reported, it appears that the addition of tryparsamide did not improve the patient's opportunity for a successful outcome. This is demonstrated by the fact that the failure rate is not increased in those patients who did not receive tryparsamide. Furthermore, those patients who received either malaria or penicillin did appreciably better than those who received arsenotherapy.

jections of the drug. There was definite improvement in the cerebrospinal fluid of 62 of these patients, and of these all but 5 patients, or 57, had received in addition 75 injections of trivalent arsenicals and bismuth, and several had a course of malaria therapy. There were 38 patients (38%) who failed to improve.

There were 122 patients who received no tryparsamide but had a minimum of 75 injections of trivalent arsenicals, including old arsphenamine, neoarsphenamine and arsenoxide, plus bismuth; 86 patients (70%) improved. A total of 36 patients (30%) failed to exhibit satisfactory cerebrospinal fluid changes. In essence, these patients received the same trivalent arsenotherapy and bismuth as

TABLE 1.—TOXICITY OF TRYPARSAMIDE

Type of neurosyphilis	Patients treated	Minor reactions*	Visual reactions		Total reactions
			Transient	Permanent	
Asymptomatic . . .	139	15 (11%)	28 (20%)	17 (12%)	60 (43%)
Tabes dorsalis . . .	126	22 (17%)	32 (25%)	27 (21%)	81 (64%)

* Includes nitritoid crises, gastro-intestinal and cutaneous reactions.

ASYMPTOMATIC NEUROSYPHILIS. In the evaluating of any therapeutic agent in the treatment of asymptomatic neurosyphilis, 2 factors must be considered: (1) the ability of the treatment to induce changes of the various cerebrospinal fluid components toward normal; and (2) maintenance of the asymptomatic state, that is, prevention of clinical evidence of symptomatic neurosyphilis.

Laboratory Evaluation. Because of the frequency of overlapping treatment schedules, each chart was evaluated as follows:

(*a*) Was cerebrospinal fluid improved on 25 or more injections of tryparsamide.

(*b*) Did cerebrospinal fluid fail to improve on 25 or more injections of tryparsamide.

(*c*) Of those who improved on the tryparsamide therapy, how many received an additional course of at least 75 injections of trivalent arsenical and bismuth.

Of the 139 patients in the asymptomatic neurosyphilis group who received tryparsamide, 100 patients received at least 25 in-

the group who received tryparsamide. It may be seen that the addition of tryparsamide did not alter the final outcome appreciably, since there was improvement in 62% of those who received tryparsamide, in contrast to the 70% who did not receive it. This indicates that those patients who received the pentavalent drug and risked the toxicity associated with it, did not have any greater chance of successful outcome.

Twenty-six patients with asymptomatic neurosyphilis underwent a course of malaria therapy with subsequent improvement in the cerebrospinal fluid of 21, a failure rate of 19%. In the malaria treated series, evaluation was done prior to the initiation of chemotherapy.

In a recent study undertaken at this hospital,[14] 34 patients with asymptomatic neurosyphilis were treated with sodium penicillin. Most of these patients received 4 million units of the drug during a 2 weeks period. Many had failed to respond to previous antisyphilitic therapy.

It was found that, of the 34 patients, all but 5 had responded satisfactorily; 1 year after instituting penicillin therapy, the cells, protein, and colloidal gold curve were normal, and the titer of the Wassermann reaction had dropped appreciably. The failure rate is 15%. This should be compared to the failure rate of 19% after malaria therapy, of 30% following trivalent arsenobismuth therapy, and of 36% in patients who received tryparsamide in addition to the trivalent arsenotherapy. Although it is impossible to determine the exact worth of tryparsamide from these data, it is readily apparent that the addition of the pentavalent drug did not help the patients who received it.

Clinical Evaluation. Determination of the therapeutic value of any agent used in asymptomatic neurosyphilis is essentially an evaluation of its ability to induce changes in the cerebrospinal fluid, except for subsequent studies to determine how many patients developed symptomatic neurosyphilis. Very few patients of those followed developed clinical evidence of neurosyphilis. One reason for this may be that almost all patients with a strongly positive cerebrospinal fluid (elevation of the cell count, total protein and colloidal gold curve) were given either malaria or penicillin. This vigorous attack on those patients who were the more like candidates for clinical neurosyphilis precludes any analysis of the comparative value of the antisyphilitic agents used. For the most part, patients who received tryparsamide and trivalent arsenicals had relatively inactive cerebrospinal fluids with essentially normal cells, protein and gold curve.

Tabes Dorsalis. *Laboratory Evaluation.* Of 81 patients with tabes dorsalis treated with 25 or more injections of tryparsamide, there was no improvement in the cerebrospinal fluids of 34 (42%). There were 109 tabetic patients who received at least 75 injections of trivalent arsenical and bismuth without tryparsamide. Of this group, 42 did not improve (38%). The same statement may be made about those patients with tabes dorsalis that was made about the group with asymptomatic neurosyphilis; namely, that the group who had tryparsamide received approximately the same amount of trivalent arsenobismuth therapy as the group who did not receive tryparsamide. Again, the number of failures is approximately the same (42% with tryparsamide and 38% without tryparsamide). It may be concluded that tryparsamide had no more influence in the cerebrospinal fluid in patients with tabes dorsalis than it did in patients with asymptomatic neurosyphilis.

A total of 50 patients were given a course of malaria with no subsequent improvement in the cerebrospinal fluid of 14 (28%). In the penicillin treated group of tabetics, there were 22 patients who received 4 million units and were followed at least 12 months. All but 3 cases obtained a satisfactory cerebrospinal fluid response, a failure rate of 14%.

Clinical Evaluation. The ability of tryparsamide and of other antisyphilitic agents to influence the complaints of tabes dorsalis is considered. These symptoms include shooting pains, ataxia, urinary incontinence, diplopia, gastric crises and sexual impotency. Trophic changes, such as Charcot joints and skin ulcers, are not included. Detailed evaluation will appear in a subsequent publication. At present, these symptoms are grouped according to the therapy administered. There were a total of 84 symptoms among the 81 patients who received 25 or more injections of tryparsamide. There was no alleviation of 54 symptoms (64%). When the group of patients who received only 75 injections of combined arsenobismuth therapy and no tryparsamide therapy was investigated, it was found that 67 of 135 symptoms (50%) were undiminished. A smaller group of patients who received malaria complained of 51 symptoms; 18 complaints were unaltered (35%). In the group who received 4 or more million units of penicillin, there were 65 complaints, with no improvement

in 23 (33%). The ability of tryparsamide to relieve symptoms in tabes dorsalis is no greater and probably is less than that of other forms of antisyphilitic therapy. Many patients who were given malaria and penicillin with satisfactory results had previously failed to be helped by either trivalent or pentavalent arsenotherapy. It is not possible to prove from this material that tryparsamide is a drug of little or no value. However, it is evident from this study that the *addition of tryparsamide* did not enhance the patient's opportunity for a successful outcome in terms of improvement in cerebrospinal fluid and/or relief of symptoms.

Discussion. Consideration of pharmacologic studies suggests that little value can be expected from tryparsamide as a therapeutic agent in the treatment of syphilis. The drug possesses very little spirochetocidal activity when compared to the trivalent arsenicals. Experimental data of Hogan and Eagle indicate that the arsenicals are only therapeutically effective in proportion to their ability to be bound by the parasite, and this activity depends on combination with essential sulfhydryl groups in the pathogenic organism. Since pentavalent arsenicals (as tryparsamide) are unable to unite with these physiologically active sulfhydryl groups until reduced to the trivalent forms (as arsenoxide), the rationale for the use of tryparsamide is open to question. Because more than half of the drug administered is excreted essentially unchanged in the urine within 6 hours, and between 80 and 90% within 24, there is little time for this reduction of the pentavalent form to the therapeutically active trivalent form. In contrast to the rapid rate that the pentavalent drugs diffuse through the kidney, the arsenoxide drugs (mapharsen, clorasen, phenarsen) are retained by the patient. The optimum rate of excretion, according to Voegtlin and Thompson[34] insures sufficient time for combination of drug and parasite, but not sufficient time to injure the tissues of the host. Moreover, no satisfactory evidence has been advanced to justify the assumption that tryparsamide possesses greater penetrability or affinity for the central nervous system than the arsenicals of lower valency.

Except for its tendency to produce toxic amblyopia, tryparsamide is the least toxic of the arsenicals used in the treatment of syphilis. This finding is in keeping with the fundamental mechanism of the mode of action of chemotherapeutic agents as outlined by Ehrlich.[8] He postulated that these agents are effective only if bound by the parasite, and the toxic activity is due to combination of the chemical agent to the tissues of the host. The number of cases of cutaneous, gastro-intestinal and nitritoid reactions caused by tryparsamide are small when compared to the minor and major reactions caused by the trivalent arsenicals. This absence of systemic toxicity suggests failure of tryparsamide to combine with the tissues of the host just as absence of therapeutic efficacy suggests failure of the pentavalent drug to combine with the parasite. In general, arsenicals are therapeutically active only to the degree that they are bound to the sulfhydryl group of the parasite and the host, and the differences in toxicity of these compounds is due to their varying affinity for tissues. Recently Hogan and Eagle[11] confirmed the postulation of Ehrlich by experimental studies. It is evident that what is considered therapeutically beneficial activity for the host represents toxic activity toward the parasite. This explains why both the toxicity of the pentavalent drugs (except of visual damage) and the therapeutic effects are of a low order.

In spite of the low toxicity of tryparsamide in terms of minor reactions, its tendency to induce damage to the optic nerves is great. In the series reported in this paper, 45% of all tabetics who received any tryparsamide experienced subjective and transient symptoms of optic nerve damage. In spite of apparently adequate precautionary measures, 20% of the tabetics progressed to permanent dam-

age characterized by disk pallor and restriction of visual fields. In all likelihood, this toxic manifestation of tryparsamide is not similar to the minor reactions, but represents a unique vulnerability of the optic nerve to the drug. The greater incidence of tryparsamide amblyopia in tabetics may be associated with subclinical damage to the optic pathways caused by syphilis.

It is difficult to evaluate the satisfactory results previously ascribed to tryparsamide. There are several factors which may be significant. Previous workers have found that good effects are obtained only by prolonged use of the drug, usually in conjunction with mercury and more recently with bismuth. It is likely that these benefits are dependent in part on the concurrent use of the heavy metal, in part on the activity of the trivalent arsenical which results from reduction of the pentavalent drug, and in part on the spontaneous changes that occur in cerebrospinal fluid with the passage of time. Another factor that handicaps interpretation in retrospect is the fact that, not uncommonly, patients were previously treated with agents of proved value such as trivalent arsenicals and malaria, but the good results were presumed due in whole or in part to tryparsamide.

Because the patients treated at the New York Hospital Clinic were so frequently given either concurrent or overlapping therapy, it is impossible from this study to prove that tryparsamide is an ineffective drug, but it is possible to show that it is not superior to the other antisyphilitic agents to which it is compared. It is possible to prove the effectiveness of both malaria and penicillin. Justification for the use of an agent such as tryparsamide which not infrequently causes partial or complete blindness would exist if no satisfactory alternative therapy were available and if proof of its therapeutic efficacy were irrefutable.

Summary and Conclusion. 1. Because pharmacologic studies show that pentavalent arsenicals, including tryparsamide, are not therapeutically effective until reduced to the trivalent form and do not possess greater penetrability or affinity for the central nervous system than the trivalent drugs, one cannot expect that tryparsamide will be an effective chemotherapeutic agent for the treatment of syphilis.

2. Tryparsamide often causes permanent visual damage in spite of detailed precautionary measures. This is especially true in patients with tabes dorsalis.

3. Considerable variation in the therapeutic results attributable to tryparsamide is evident throughout many reports. Patients with neurosyphilis treated in this clinic failed to substantiate the reported therapeutic efficacy of the drug.

4. There are alternative methods for treating all forms of neurosyphilis in which tryparsamide is said to be of value, and none of these regimens is as dangerous as one employing tryparsamide.

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RADIOLOGY

UNDER THE CHARGE OF

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THE MEDICAL USE OF RADIOACTIVE ISOTOPES

I. RADIOACTIVE ISOTOPES IN HEMATOLOGIC DISTURBANCES AND NEOPLASMS

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RADIOPHOSPHORUS. Radiophosphorus was the first radioactive isotope to be employed in the treatment of disease. Lawrence and his associates, as early as 1936, studied the possibilities of employment of this substance therapeutically in leukemia and allied diseases. Since then, the use of radiophosphorus as a therapeutic agent has been studied in a variety of conditions. Although the total number of patients treated with radiophosphorus is not large, sufficient time has elapsed to permit certain tentative conclusions to be drawn concerning the value and the limitations of this form of therapy.

Radiophosphorus (P^{32}) is prepared in the cyclotron by the bombardment, at high velocity, of ordinary red phosphorus (P^{31}) with deuterons (nuclei of heavy hydrogen). Neutrons are forced into the nuclei of some of the atoms, increasing the mass of such atoms by 1 (17 neutrons and 15 protons). Thus, the atomic weight of the new substance becomes 32. However, the number of protons and electrons in the atom is not changed, and since the chemical reactions of an atom are dependent on the number of electrons the atom contains, radiophosphorus behaves chemically in the same manner as does ordinary phosphorus. Consequently, when it is introduced into the living organism, radiophosphorus enters into all phases of phosphorus metabolism.

Radiophosphorus is unstable; it disintegrates at a constant rate through the emission of a beta ray. The emission of the beta ray occurs at the moment a neutron in the nucleus is changed to a proton. Although the mass of the new atom is not changed, the nucleus now contains 16 protons and 16 neutrons. Since the number of electrons equals the number of protons in an atom, a new substance chemically different from radiophosphorus is created. In this case, it is stable sulfur (S^{32}). Radiophosphorus does not emit alpha and gamma rays.

The rapidity of decay of any radioactive substance is expressed by the time required for half of an initial stock of atoms to disintegrate. This is called the "half-life" of the isotope. In the case of radiophosphorus, 35 of every 1,000,000 atoms undergo spontaneous transformation to stable sulfur each minute, giving radiophosphorus a half-life of 14.3 days.

The radioactivity of an isotope is measured in terms of millicuries. One millicurie (mc.) is that amount of radioactivity produced by disintegration of 37,000,000 atoms per second. One microcurie (μc.) is $\frac{1}{1000}$ of 1 mc.

Radiophosphorus can be administered to patients, orally or intravenously, in the form of a phosphate. Usually, it is given in the form of monobasic or dibasic sodium phosphate. When the oral route is em-

ployed, from 15 to 50% of the amount administered is excreted in the urine and feces during the first 6 days.[10,29] Most of this loss is caused by lack of absorption of the phosphate in the gastro-intestinal tract. As a general rule, it is safe to assume that 25% of the amount of radiophosphorus administered orally will be lost in the stool, and that 75% will be absorbed.

When radiophosphorus is administered intravenously to normal persons, from 25 to 50% of the quantity injected is excreted during the first 6 days. In leukemic and polycythemic patients, the excretion of the isotope is less than that which occurs in normal persons, varying from 5 to 25% of the amount injected over a similar period.[10,29] Thereafter, the rate of excretion in all persons falls to 1% or less per day. When the intravenous route of administration is employed, most of the loss occurs in the urine.

After administration, radiophosphorus is rapidly and selectively withdrawn from the blood by certain tissues and cells. According to Reinhard and his associates,[29] the selective uptake of phosphorus by cells is dependent principally on 3 factors: (1) the total amount of phosphorus in exchangeable form in the tissue, (2) the rate of turnover of phosphorus by the tissues and (3) the rate at which new tissue is formed.

As stated previously, in normal animals radiophosphorus is deposited in large amounts in bone and bone marrow, and in somewhat smaller quantities in the liver, spleen and lymph nodes. In the presence of pathologic conditions, the uptake of radiophosphorus has been found to be much higher in rapidly metabolizing neoplastic tissues than it is in the same type of tissue in a normal state of growth.

In leukemia and in polycythemia, the isotope is taken up rapidly by both circulating erythrocytes and leukocytes during the first 24 hours after the administration.[9–11,34] The concentration in the erythrocytes then decreases sharply, while the concentration in the leukocytes decreases more slowly and the radiophosphorus is retained for much longer periods and in greater quantities than in the erythrocytes.

In certain diseases of the hematopoietic system, the distribution of radiophosphorus in various organs and tissues after it has been administered has received considerable attention.[4–6,20,29,33,36] The studies of Reinhard and his associates[29] were especially illuminating in this regard. In chronic myelogenous leukemia, greater activity was found in the bone marrow than in any other organ, whereas in chronic lymphatic leukemia, the liver, spleen and lymph nodes in most instances contained a higher concentration of radiophosphorus than did the bone marrow. In acute leukemia or leukosarcoma, variable results were observed, but in general the liver and spleen accumulated more of the material than did the bone marrow. In most cases, however, the concentration of radiophosphorus was found to be lower in lymph nodes than in bone marrow, liver, spleen or kidney. In lymphosarcoma and actively progressing Hodgkin's disease, Erf and Lawrence[8] found as great a retention of radiophosphorus in lymph nodes as in the liver and kidney. However, in 1 case of Hodgkin's disease in which the lymph nodes had become densely fibrotic, the uptake of radiophosphorus was lower than that in the other tissues assayed.

Data concerning the differential uptake of radiophosphorus in various organs in the presence of other diseases also have been accumulated. These diseases include melanoma and melanosarcoma, seminoma, neuroblastoma, Ewing's sarcoma, fibrosarcoma, reticulum-cell sarcoma, multiple myeloma and metastatic carcinoma. In general, the distribution of the substance among different organs and tissues of the body depends on the type of neoplastic disease present, the degree of infiltration of an organ by abnormal cells and the rate of growth of these cells. Tissues which have a high concentration and a rapid turnover of stable phosphorus also take up higher concentrations of radiophosphorus than do normal tissues.

The depth of penetration of the beta rays emitted by radiophosphorus varies in different tissues, having a maximal range of penetration of approximately 7 mm.[29] The rays have the capacity to produce ionization in tissues, and therefore the radiation effects are basically similar to those of Roentgen rays and radium.

Because radiophosphorus is deposited predominantly in bone and bone marrow, the effect of the radiation produced by this agent is greater on the bone marrow than on other hematopoietic organs. Consequently, this form of therapy has been applied to diseases in which the bone marrow is involved primarily by a pathologic process, or to diseases in which the marrow is extensively involved, even though the primary site of the disease is in other organs. Since diseases of the blood fall into these 2 categories, the greatest therapeutic trial of radiophosphorus has been in the field of hematology. To date, radiophosphorus has seemed to be the treatment of choice in polycythemia vera.

Polycythemia Vera. *Method of Treatment and Dosage.* For intravenous administration, a single injection of 3 to 7 mc. of radiophosphorus is given, the size of the dose depending on body weight, the age of the patient, and the severity of the disease. Approximately 25% of patients treated with radiophosphorus obtain satisfactory remission from a single injection.[17] In patients in whom remission is not induced by the first injection, subsequent doses of 3 to 7 mc. may be injected at intervals of 8 to 12 weeks. The administration of radiophosphorus at intervals shorter than 8 weeks is inadvisable. Inasmuch as the life span of the erythrocyte of human beings has been shown to be 3 to 4 months, and since aged erythrocytes are removed slowly from the circulation, the degree of inhibitory action of the isotope on erythropoiesis cannot be assessed with reasonable accuracy in periods less than 8 weeks. Second or third injections of radiophosphorus can be carried out safely, provided that the erythrocyte count has not fallen below 6,000,000 cells per c.mm. or the cell volume percentage below 55, and provided that marked suppression of the leukocyte or platelet levels has not occurred after the initial injection. If the erythrocyte count is less than 6,000,000 or the cell volume percentage is less than 55, further treatment with radiophosphorus should be withheld until a relapse occurs. If additional treatment with the isotope is indicated by the fact that the erythrocyte count remains above 6,000,000 or the cell volume % remains above 55, and if a marked decrease in the number of leukocytes or platelets occurred after the first injection, then smaller doses than were employed in the first instance should be given.

Because a decrease in erythrocyte, hemoglobin and hematocrit values does not occur, as a rule, within less than 6 to 8 weeks after the initial injection of the isotope, and since patients who have uncontrolled polycythemia vera run an increased risk of thrombosis, some observers[17,18] recommend that venesection be performed repeatedly prior to the initial injection of radiophosphorus.

Results. Since Lawrence[24] first reported the successful treatment of 2 patients who had polycythemia vera with radiophosphorus, the results of treatment in 273 cases have been reported.[3,7,14,17,18,24,26,35] Detailed follow-up data have been published by Reinhard and associates[29] and by ourselves[17] in 84 cases. Satisfactory hematologic remission was obtained in approximately 85% of the 84 cases; partial remission was induced in the remaining 15%. A decrease in values for leukocytes and platelets preceding or accompanying the decrease in erythrocytes also occurred in the majority of cases. Subjective improvement occurred in cases in which a substantial decrease in values for erythrocytes and a reduction in blood volume were noted. In many cases, the degree of symptomatic relief was pronounced, resulting in restoration of a sense of normal well-being. Except in occasional cases of long-standing disease

in which the spleen had become enormously enlarged, firm and presumably fibrotic, treatment resulted in reduction in the size of this organ, often to the point at which it no longer could be palpated. Generally, when hepatomegaly was present, some reduction in the size of the liver occurred. Other objective signs, such as ruddy cyanosis, conjunctival injection and distention of retinal venules also either abated or disappeared.

Sufficient time after the institution of radiophosphorus therapy in polycythemia vera has not elapsed to permit a definite analysis of the duration of the remission induced with this form of treatment. However, Reinhard and associates,[29] Erf[3] and ourselves[17] reported comparable results with remission which endured 5 months to $4\frac{1}{2}$ years. Among the 84 patients treated by Reinhard and by ourselves, 62 obtained remission which lasted more than 6 months, 25 obtained remission which lasted more than 1 year, and 10 obtained remission which lasted more than 2 years. However, the disease of many of these patients was still in remission at the time the reports were published, so that further observation over a prolonged period will be necessary to determine how long remission will last. When polycythemia vera recurs, remission can be induced a second time by the administration of more radiophosphorus.[3,17,29]

Whether or not radiophosphorus therapy significantly prolongs the lives of patients who have polycythemia vera has not been determined. Detailed data on the duration of life in a large series of patients, either untreated or treated by means of venesection, the administration of phenylhydrazine or Roentgen radiation, are not available. However, in 36 of 163 cases of polycythemia vera in which follow-up data could be obtained, Tinney, Giffin and 1 of us (Hall)[30] reported on 32 who lived more than 5 years after the diagnosis had been established, 28 who lived more than 10 years, 8 more than 15 years, and 4 more than 20 years. Two patients living 5 years after the diagnosis had been made had not been treated; all others had received treatment of some kind, although in many instances treatment had been inadequate or had been discontinued voluntarily by the patient. The course of the disease, therefore, is chronic and often of long duration. Death most commonly results from vascular complications (coronary or cerebral thrombosis or pulmonary embolism), hemorrhage, intercurrent infection, or a terminal "leukemic" blood picture associated with anemia. Erf[3] recently published data on the causes of death among 214 patients who had polycythemia and who had been treated with radiophosphorus at various institutions in this country. Thirteen deaths were recorded, 5 in which the terminal blood picture was indistinguishable from that of myelogenous leukemia; 3 in which there were malignant tumors; 3 in which there was intercurrent infection; 1 in which there was hypoplastic anemia and 1 in which there was gastric hemorrhage. The absence of venous thrombosis as a cause of death in the aforementioned group would appear to be significant. Data concerning 102 additional patients with polycythemia vera treated with radiophosphorus, not included in Erf's report, have shown acute leukemia to be the cause of death in 2, congestive heart failure in 1, and probable coronary thrombosis in 1.[16] Acute leukemia, therefore, has been the principal cause of death among polycythemic patients treated with radiophosphorus to date. The incidence of leukemia in the treated group is 2.2% (7 of 316 cases), but this figure is well below the percentage of 10 as reported by Tinney and associates[31] as dying with a blood picture indistinguishable from that of chronic myelogenous leukemia in a series of 163 cases of polycythemia vera studied prior to the institution of radiophosphorus therapy. Since a longer period of time may increase the incidence of acute leukemia, eventually this may prove to be a less valuable form of treatment than it appears at present.

Complications. The complications encountered when this form of therapy is used are largely hematologic, in the form of thrombocytopenia, leukopenia and anemia. These complications are comparatively common. Among the 54 cases in our series, leukopenia developed in 54%, thrombocytopenia in 39% and anemia in 18%. Any one of them was found to occur singly or in combination with one of the others, but in only 1 case were thrombocytopenia, leukopenia and anemia observed simultaneously.

Considerable variation in the period of time elapsing between the administration of the isotope and the development of the complication was noted. Leukopenia developed within 2 weeks to 6 months after the injection of radiophosphorus, thrombocytopenia within 3 weeks to 2 months, and anemia within 2 to 10 months. The anemia and leukopenia were of relatively short duration, and no complications were noted as a result of their development. The thrombocytopenia, when it developed, tended to last somewhat longer, extending over periods of 4 to 8 weeks. The only hemorrhagic phenomenon observed was the development of petechiæ on the extremities in 2 cases. No deaths as a result of the aforementioned complications have been reported.

LEUKEMIA. Administration of radiophosphorus in leukemia and allied diseases differs from that in polycythemia vera. An attempt is made to minimize the inhibitory effect of the isotope on the formation of erythrocytes and blood platelets while, at the same time, a maximal depressant effect on leukopoiesis is being obtained. This can be accomplished by the administration of radiophosphorus twice a week according to the "fractional method" of Low-Beer, Lawrence and Stone,[26] until the desired result has been obtained. An initial dose of 1 to 3 mc. usually is administered. Thereafter, the size of the biweekly injections varies from 0.5 to 2 mc. Treatment must be highly individualized because of the great variation in response shown by the different patients.

Reports on the use of radiophosphorus as a therapeutic agent have been published concerning 136 patients with chronic or subacute myelogenous leukemia,[2,12,14,17,20,25,29] 98 patients with chronic or subacute lymphatic leukemia[2,12–14,17,20,24–26,29,35,37] and 109 patients with various types of acute leukemia.[2,12,17,20,22,23,26,29,35,37] Significant beneficial results have not been observed in any of the cases of acute leukemia. In the chronic forms of the disease, results comparable to those secured with Roentgen radiation have been obtained. Clinical and hematologic remission has been induced in a high proportion of patients, but published reports do not indicate that the duration, either of individual remission or of life, is greater than that noted after Roentgen ray therapy.

The results of treatment in chronic myelogenous leukemia appear to be somewhat better than those obtained in chronic lymphatic leukemia.[12,29] A progressive decrease in leukocyte values, often accompanied by an increase in values for hemoglobin and erythrocytes, reduction in the size of the spleen and liver, and symptomatic improvement, occurs in most patients, except those in the terminal stage of the disease.

In chronic lymphatic leukemia, the number of patients who obtain satisfactory remission is somewhat lower than it is in chronic myelogenous leukemia. Although a reduction in the leukocyte count and improvement in the blood picture are observed in a significant proportion of patients, less recession of the patient's symptoms and anemia occurs. Some reduction in the size of lymph nodes and of the spleen commonly is observed, but in most cases it also appears to be less than that obtained by Roentgen ray radiation.

On the basis of data collected by various observers, the administration of radiophosphorus in the chronic leukemias has been found to bring about hematologic remission and clinical improvement in a

manner comparable with that obtained with Roentgen ray therapy. However, the use of this isotope does not cure the disease. The chief advantages of this form of treatment are the ease of administration and the absence of radiation sickness. The principal disadvantages are the greater length of time required to bring about the desired therapeutic result and the greater risk of injury to the bone marrow, especially with regard to inhibition of the formation of blood platelets to the point at which serious hemorrhagic complications might develop. In carefully selected cases, once remission has been induced by means of Roentgen ray radiation, radiophosphorus has been found to be effective in holding leukocyte counts at or near normal levels for long periods.[16,17] Used in this way, radiophosphorus therapy eventually may prove to be a useful adjunct to treatment with Roentgen rays.

Miscellaneous Diseases. From the results thus far reported, radiophosphorus therapy does not appear to be as effective as Roentgen ray radiation in Hodgkin's disease, lymphosarcoma or reticulum-cell sarcoma.[14,17,19–21,26,29,35] In myeloma it does not inhibit progression of the disease, although pain in the bones may be relieved in a high proportion of cases.[12,14,17,20,26,29,35] In osteogenic sarcoma, malignant melanoma, carcinoma of the gall bladder, disseminated carcinoma of the breast, lympho-epithelioma, mycosis fungoides and xanthomatosis, radiophosphorus is not a satisfactory therapeutic agent.[14,20,29]

Summary of Radiophosphorus Section. In summary, on the basis of present evidence, radiophosphorus therapy provides an effective means for the control of polycythemia vera. Remission, often of long duration, can be induced in a high proportion of cases. The chief advantages of this form of treatment appear to be the ease of administration, the absence of radiation sickness and symptoms of toxicity and the simplicity with which the dose can be controlled. The principal disadvantages are the cost of the material and the fact that the bone marrow may be injured seriously in the case of overdosage or an unusual sensitivity of the marrow to therapeutic doses. Moreover, the possibility that radiophosphorus may cause terminal acute leukemia must be borne in mind. In the chronic leukemias, radiophosphorus induces remission similar to that produced with Roentgen rays, but therapy with this isotope apparently has no particular advantage over the latter form of treatment and requires a longer period to bring about the desired result. In multiple myeloma, radiophosphorus relieves pain in bones in a significant proportion of cases, but does not inhibit the systemic progression of the disease. In the lymphomas, radiophosphorus therapy appears to be less effective than Roentgen ray treatment, and in acute leukemia, metastatic tumors, mycosis fungoides and xanthomatosis, the isotope is ineffective as a therapeutic agent.

Radiostrontium. Although the most extensive studies of radioactive elements in the experimental laboratory and in the human being have been carried out with radiophosphorus, other radioactive elements have been produced and the use of them in both animals and human beings has been investigated. Since radiostrontium is picked up readily by growing bone, use of it in animals and human beings has been investigated; but because of its half-life of 180 days and its weak available activity, its therapeutic use has been slight.

The similarity between calcium and strontium led Pecher[28] to investigation of radiostrontium (S^{89}) which has a half-life of 55 days and emits beta rays similar to those of radiophosphorus. It has been found that the dose of radiation afforded by radiostrontium is highest in the regions in which an osteoplastic process exists, as in osteogenic sarcoma and the osteoplastic metastasis of carcinoma of the prostate gland.

Radiostrontium lactate is readily concentrated in growing bony tissue. Tread-

well and associates[32] found that the high uptake of strontium occurs in areas in which new bone is being laid down, whether the new bone is normal or neoplastic. They felt that radiostrontium would constitute a valuable tool in the study of the healing of bone after experimental fractures.

Radio-iron. Radio-iron employed as a tracer substance has proved of value in the study of iron metabolism and the formation and destruction of the blood. When tracer doses of radio-iron are used, a group of iron atoms can be traced throughout the body by means of a Geiger-Müller counter. Since the material used in tracer doses is without danger to human beings, this material can be used safely in both normal persons and persons who have various blood dyscrasias.

Many very interesting studies have been carried out in an attempt to explain the absorption of iron. It has been shown that iron is absorbed by the body only when it is needed to replace depleted iron reserves.

Radio-iron has been used to determine the true erythrocyte cell volume of the blood, which was found to be approximately 8.5% lower than the centrifuge hematocrit volume.[1]

Peacock and associates,[27] using 2 radioactive isotopes of iron, F^{59}, with a 47 day half-life, and F^{55}, with a 5 year half-life, have carried out tracer studies and have presented methods of utilization of these substances in experimental medicine.

Gibson and associates[15] published a method of determination of the circulating erythrocyte volume by the use of 2 radioactive isotopes of iron. This method gives an absolute measure of the circulating erythrocyte, a measure which is independent of the venous, arterial or auricular hematocrit reading. The method has been applied to the study of normal erythrocyte cell volume as well as experimental shock, arterial occlusion, burns and bacillary toxins.

Radiosodium. One isotope of radiosodium, which has a half-life of 14.8 hours, has been used in the treatment of leukemia. This material distributes itself throughout the extracellular and intracellular fluid, and maintains a nearly constant level of radiation in the blood stream. It emits beta rays and hard gamma rays, and therefore acts very much like spray Roentgen therapy, with uniform radiation of the body.

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RADIOLOGY

UNDER THE CHARGE OF

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THE MEDICAL USE OF RADIOACTIVE ISOTOPES

II. RADIO-IODINE AND THE THYROID

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Because of the specific affinity of the thyroid for iodine and the specific rôle of iodine in the formation of thyroid hormone, it is not surprising that radio-iodine has been applied promptly and widely to the study of problems in thyroid physiology and thyroid disease. At least 8 different radioactive isotopes of iodine have been described and at least 4 of these have been used in biologic investigations.[15] However, I^{131} (half-life, 8 days)* and I^{130} (half-life, 12.6 hours) or a mixture of both have been utilized in most investigations. Both of the isotopes give off relatively strong beta rays and relatively feeble gamma rays. They are prepared by bombardment of tellurium with neutrons in the cyclotron. Much of the radio-iodine which has become available to medical investigators was prepared in the cyclotrons of the Massachusetts Institute of Technology and the University of California. Without the excellent collaboration and coöperation of the staffs of these and other laboratories, this field could not have developed so rapidly.

Physiologic Applications. Hertz[11] in 1937 was first to investigate the possibilities of radio-iodine as an indicator in thyroid physiology. He used the tracer technique.†

Hertz[12] and many other subsequent investigators found that the thyroid collected iodine with avidity and that the degree of such avidity for iodine could be correlated with various histologic and physiologic states of the thyroid. Iodine deficiency, administration of potassium thiocyanate,[19] and soy bean diet all increased the affinity of the thyroid for iodine.[13] The previous administration of iodine or of thyroxin and hypophysectomy

* Iodine^{131} designates iodine with atomic mass of 131 to distinguish it from natural iodine (mass, 127) By "half-life" is meant the time required for half of any quantity of the isotope to disappear.

† "Tracer technique" refers to the use of radioactivity to trace the course of minute quantities of material through various reactions. The chief value of such methods lies in their application to the study of metabolic processes under conditions of physiologic equilibrium. Many problems, especially those involving rates of collection and turnover, can be approached now for the first time by means of this technique.

were among the factors which reduced it. Thiouracil and related goitrogenic substances promptly and markedly decreased iodine collection before any other effects of these agents were evident.[19] Chaikoff and his associates[2,17] have used radio-iodine in *in vivo* and in *in vitro* studies to examine the rate and mode of formation of diiodotyrosine and thyroxin. Other studies have dealt with the mode of action of thyrotropic hormone, qualitative differences in the action of various goitrogens, functional maturation of embryonal thyroid tissue and numerous related problems.

Clinical Investigations. While its use in studies involving experimental animals has been productive, radio-iodine offers its greatest promise in the investigation of thyroid function in man. Hamilton and Soley[5] were the first to study the behavior of radio-iodine in man. Hertz and his colleagues,[8] Rawson[18] and others also have explored the method extensively. Radio-iodine is collected by the thyroid in substantial amounts. Most of the iodine not collected by the thyroid is excreted in the urine; only insignificant amounts appear in the feces. Euthyroid persons excrete up to 80% of a given dose in the urine; myxedematous patients, up to 95%, and persons who have untreated thyrotoxicosis, a much smaller percentage than those who have normal thyroids.[6]

Hamilton and Soley[6] have measured directly the collection of iodine in the thyroid by placing a Geiger-Müller counter over the thyroid. They found that both the collection of iodine by the gland and the subsequent disappearance from the gland can be followed in this way. Despite its technical limitations, this procedure offers great promise. When it can be supplemented by an accurate method for measuring radio-iodine in blood in addition to the measurement of urinary excretion, it will be possible to examine more precisely than heretofore the altered dynamics of iodine metabolism in thyroid disease.

Hamilton and Soley[7] have also pioneered in applying the technique of autoradiography* to the study of surgically removed thyroid tissue. By this means they and others investigated the microscopic distribution of radio-iodine in the thyroid and were thus able to correlate the structure of the gland with the distribution of iodine.

The application of tracers of radio-iodine to the study of patients is somewhat limited by the necessity of avoiding doses of radiation which are sufficient to modify thyroid function because of 2 factors: (1) the risk of producing artefacts which may be misinterpreted, and (2) the hazard of exposing the thyroid to undesirable quantities of radiation. All of the tracer studies reported so far involve quantities of radiation in the thyroid which substantially exceed the arbitrary tolerance dose of 0.1 r per day, a dose generally accepted as permissible in work with Roentgen rays and radium.

Radio-iodine probably will find its chief use as a tool for the study of thyroid function. However, it also has some promise as a therapeutic agent. Hertz and Roberts[9] in 1942 reported preliminary observations made in 10 cases of exophthalmic goiter treated with radio-iodine. Hamilton, Lawrence and Soley[4,5] also reported early results with the treatment of exophthalmic goiter. While both groups were encouraged by their trials, they did not publish sufficient detail for an adequate appraisal of the procedure. Hertz and Roberts[10] recently have reported a detailed follow-up study of their experience in treating 29 patients, and Chapman and Evans[1] have published similar data concerning an additional series of 22 cases. Remission of hyperthyroidism was observed in a majority of cases in both series. In the group of patients treated by Chapman and Evans the average dose of radia-

* An autoradiograph is made by applying a sensitized emulsion to a thin microscopic section of thyroid tissue, which previously had collected radio-iodine, for a sufficient time to allow the radiation from the radio-iodine to expose the emulsion. The resulting pattern discloses the distribution and density of the radio-iodine in the tissue.

tion given was 2 to 3 times as much as that used by Hertz and Roberts. Of the 22 patients in Chapman and Evans' report, 20 were relieved of hyperthyroidism; in 4 of the 20 cases myxedema developed. Mild reactions resembling radiation sickness occurred in 6 cases.

So far, it appears that the possibilities of treating thyroid cancer with radio-iodine are very limited. As Hamilton was first to point out,[7] lack of success is due to the fact that most malignant lesions of the thyroid are unable to collect or store iodine. However, 3 cases have been reported in which thyroid carcinoma and distant metastatic lesions collected radio-iodine in amounts sufficient for treatment.[3,14] In 1 case prolonged treatment with radio-iodine effected a remarkable arrest of widespread bony metastatic lesions.[20] It is reasonable to assume, therefore, that a few malignant lesions of the thyroid actually will prove amenable to this form of treatment. Even though, as seems probable, such cases prove to be a very small proportion of thyroid malignancies, treatment with radio-iodine is sufficiently promising to justify a careful search for cases in which it might be effective.

The therapeutic application of radio-iodine is complicated by the difficulties of determining the dose of radiation received. Various aspects of this highly technical subject have been discussed by Marinelli[16] and by Chapman and Evans.[1] The biologic factors which must be known and measured in order to determine dosage include the actual weight of the thyroid gland, the quantity of a given dose collected by the thyroid and the rate at which iodine is excreted subsequently by the thyroid. The purely physical factors include the qualitative character and specific energy of the radiation of the isotope employed, as well as the half-life of the isotope. Most of the foregoing can be determined, at least approximately, but other variables cannot. These variables include variations in radiosensitivity due to varying degrees of hyperplasia or the like. On this account it seems likely that, for the present at least, dosimetry may remain on a somewhat empiric basis.

In all therapeutic studies reported thus far a mixture of radioactive isotopes of iodine consisting chiefly of I^{130} has been employed. Because of the physical limitations of the cyclotron this could be prepared only in relatively small quantities and because of its short half-life it was useful only to investigators within the immediate vicinity. In recent months, I^{131} prepared in the uranium piles of the Clinton Laboratories has become available in large quantities, and consequently it is now receiving extensive therapeutic trial. Since the physical characteristics of I^{131} are different from those of I^{130}, the problem of effective dosage is certain to be different.

It must not be thought that use of radio-iodine, either as a tool for investigation or as a therapeutic agent, is without danger. The handling of radio-iodine requires the same kind of precautions against the insidious and disastrous consequences of radiation for the patient, the physician and the technician as does the use of radium or Roentgen rays. This is particularly the case because of the penetrating character of the gamma rays. Much more information is needed concerning minimal quantities which are capable of producing radiation effects both on the thyroid gland and other organs.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 18, 1947

Hepatic Purine Nitrogen Partition in Normal and Injured Rats. By JULIUS SCHULTZ and HARRY M. VARS (Harrison Dept. of Surg. Research, Univ. of Penna.). To obtain a clearer understanding of the mechanism by which a sterile abscess affords protection against hepatic damage due to chloroform anesthesia[1], the composition of the liver under these circumstances was investigated. The purine-N and total heat-coagulable protein (Addis) of the livers of 24 and 48 hour fasted rats pooled in groups of 5 were compared with values obtained from comparable groups abscessed, anesthetized or receiving both treatments.[2] All animals had received a stock diet plus 12% casein for 2 weeks prior to the experiments.

Increased quantities of purine-N and protein were found in the livers of the injured rats. The ratios of (purine-N to total nitrogen) × 100 were significantly greater in these animals than in the fasted or fed controls. The fed and fasted rats showed a ratio of 3.6 while the abscessed animals had ratios of 4.2 without anesthesia and 3.9 with anesthesia. Anesthesia alone resulted in a ratio of 3.9.

A partition of the total purine-N into nucleotide, nucleoside, free and protein-bound purine was made. The increased levels of purine-N were due chiefly to the purine-N of the protein.

The nucleic acid content of the heat-coagulable protein was calculated from the purine-N and phosphorus contents of the protein. By subtracting this value from the total protein the quantity of the nucleic-acid-free protein was determined. The data have been expressed as the quantities present per liver of a 200 gm. rat. The increments of protein and nucleic acid of the injured animals over the amounts found in the 48 hour fasted controls are shown in Table 1. The nucleic acid composition of this increment was greater in the abscessed animals, with and without anesthesia, than in the fed or 24 hour fasted rats. These changes are characteristic of the relationships observed in tissues actively forming new protein.

TABLE 1.—PROTEIN AND NUCLEIC ACID CONTENT OF THE LIVER OF THE 200 GM. RAT EXPRESSED AS INCREMENTS ABOVE THE BASAL VALUES OF ANIMALS FASTED 48 HOURS

Treatment	Groups no.	Fast hrs.	Protein (A) mg.	Nucleic acid (B) mg.	$\frac{(A)}{(B)} \times 100$
Basal level	3	48	1145	67	5.8
Increments of Groups					
Fed	3	0	479	15	3.1
Fasted	3	24	183	−2	0.0
Abscessed	2	24	256	16	6.2
Anesthetized	3	24	255	3	1.2
Anesthetized	2	48	30	2	6.0
Abscessed—anesthetized	3	24	236	15	6.4
Abscessed—anesthetized	2	48	90	6	6.7

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Calcium Binding Property of the Serum Proteins. By A. J. Rawson, M.D., and F. William Sunderman, M.D. (Pepper Laboratory, Hosp. of the Univ. of Penna.). After separating the serum proteins by means of methanol precipitation of the globulins it is possible to measure the calcium binding property of both the albumin and total globulins without resorting to the isolation and purification of these fractions. In normal sera the average value of calcium bound to albumin was found to be 0.95 (s.e. = 0.04) mg. of calcium per gm. of albumin, and that of calcium bound to globulin, 0.74 (s.e. = 0.03) mg. of calcium per gm. of globulin.

The calcium binding property of the protein fractions was studied in sera obtained from patients suffering from multiple myeloma, lymphogranuloma venereum and sarcoidosis. It was found that in the sera of 9 out of 10 patients studied the value of the calcium binding property of albumin was increased to as much as 6 times the normal. The evidence suggests that an altered form of albumin may appear in the albumin fraction in these diseased states. It was also observed in these conditions that the value of the calcium binding property of the total serum globulins varied from the normal, and appeared to be dependent upon the predominating type of globulin present.

The hypercalcemia present in 2 of our cases of multiple myeloma was due to an increased concentration of calcium bound to protein. This increase was dependent upon 2 factors: (*a*) the increased binding power of the serum albumin, and (*b*) the increased concentrations of total globulins, with approximately normal binding property.

Pulmonary Artery Pressure in Phosgene Poisoning. By Mary Gibbon, H. D. Bruner, M.D., R. D. Boche, Ph.D., and J. S. Lockwood, M.D. (Harrison Dept. of Surg. Research, Univ. of Penna.). In order to decide whether the pulmonary edema of phosgene poisoning was due primarily to toxic endothelial damage or to elevated hydrostatic pressure, the pressures in the lesser circulation were measured in 5 cats following exposure to phosgene. The marsupialized heart preparation avoided the necessity of anesthesia and thoracotomy; the pressures were procured by means of specially designed air-damped manometers. In favorable preparations, the right and *left* atrial pressures also were measured. No evidence of raised pulmonary artery, pulmonary vein or systemic venous pressure was observed. Immediately after exposure to potentially lethal doses of phosgene, pulmonary artery and systemic arterial pressure decreased while the atrial and venous pressures remained approximately unchanged or were slightly lower; terminally all pressures tended to return toward pre-gassing levels. The operation may have facilitated development of pulmonary congestion, but these cats behaved in all respects like simultaneously gassed controls, and at autopsy their lungs were typical of phosgene poisoning.

These data exclude abnormal hemodynamics as a cause of the increased permeability of pulmonary capillaries in phosgene poisoning. Therefore, despite our inability to find histologic evidence of endothelial damage, we must postulate that such damage is present; collateral evidence supports this view.

The Effect of Carbon Dioxide on the Initial Ventricular Deflection of the EKG. By Thomas Durant, M.D., Joan Long, M.D., M. J. Oppenheimer, M.D. (Depts. of Physiology and Medicine, Temple Univ. Medical School). In the course of studying experimental air embolism,[1] the action of intravenous carbon dioxide on the EKG of the dog was investigated. Direct leads were taken from the anterior surface of the right ventricle in open chest experiments with dogs under nembutal anesthesia. When 50 cc. of CO_2 are rapidly injected into a femoral vein, the initial upward deflection is decreased in amplitude or disappears entirely in the direct

lead from the right ventricle. The S wave is slightly increased and the S–T segment is raised. The gas quickly disappears from the right ventricle (15 to 17 seconds) and the EKG returns to normal within 1 to 3 minutes. The decrease in amplitude of R is proportional to the amount of CO_2 injected. In the limb leads, the reduction of R is most pronounced in Lead 3. When 30 cc. of 1% procaine is injected the QRS interval (duration) is increased, and when the action of CO_2 is superimposed on that of procaine, the pattern from the surface of the right ventricle resembles that of right bundle branch block.

These changes are not due to dilatation of the right ventricle, as air causes greater dilatation but no change in R. The change occurs when both the sympathetic and the vagi are cut. The injection of 0.1 N HCl did not cause a lowering of R. The change failed to occur at a pH of 7.4 at one time and did occur at the same pH at another. The question is raised as to whether this change could be due to the specific action of CO_2 on the cardiac conduction system.

REFERENCE

(1.) **Durant, T., Long, J.,** and **Oppenheimer, M. J.**: Pulmonary (Venous) Air Embolism, Am. Heart J., **33**, 269, 1947.

BOOK REVIEWS AND NOTICES

ESSENTIALS OF CLINICAL PROCTOLOGY. By G. SPIESMAN, B.S., M.D., Proctologist, Mt. Sinai and Edgewater Hospitals; Consulting Proctologist, Grant, Henrotin and St. Elizabeth Hospitals. Pp. 238. New York: Grune & Stratton, 1946. Price, $4.00.

THE Reviewer has been somewhat at a loss in reading this little book to determine to what group of readers it is addressed. The description of the anatomy of the anorectal region is surely for students of medicine, but reference to "pain pills" and to the dosage of sulfadiazine and sulfauxidine in terms of the number of "tablets" to be given is surely for others than students.

The author discusses the various proctologic conditions from a practical point of view and in addition adds lists of symptoms and differential diagnosis in tabulated form.

The Reviewer cannot conscientiously say that this volume adds to our knowledge of clinical proctology, but it is possible that it may be of use to a beginning general practitioner who will meet in his practice some of the conditions here discussed. I. R.

HOSPITAL CARE OF THE SURGICAL PATIENT. By GEORGE CRILE, JR., M.D., Surgeon, Cleveland Clinic, and FRANKLIN I. SHIVELY, JR., M.D., Assistant Surgeon, Cleveland Clinic. 2nd ed. Pp. 288. Springfield, Ill.: Charles C Thomas, 1946. Price, $3.50.

THE demand for the 1st edition of this handbook has made a 2nd edition necessary within 3 years. The authors state that this is not a reference book, but it is more than likely that surgical interns and residents will find it useful as such, as well as for the purpose for which it was intended—that is, to introduce the surgical house staff to the more common procedures in modern surgical care.

It is refreshing to find in the discussion of surgical complications that the cause of the complication is always emphasized so that the young surgeon will be alert to forestall the development of such complications whenever possible.

The Reviewer recommends this handbook to all surgical residents and to the general surgeon as well. I. R.

THE TRAUMATIC DEFORMITIES AND DISABILITIES OF THE UPPER EXTREMITY. By ARTHUR STEINDLER, M.D., F.A.C.S., Professor and Head of the Department of Orthopedic Surgery, The State University of Iowa. In collaboration with JOHN LOUIS MARXER, M.D., Associate, Orthopedic Department, State University of Iowa. Pp. 515; 1048 ills. Springfield, Ill.: Charles C Thomas, 1946. Price, $10.00.

DR. STEINDLER'S book appears at an opportune time and should prove a valuable guide to the numerous members of the medical profession concerned with the problems of reconstructive surgery which have arisen from World War II. It deals with the delayed results of trauma rather than the initial care of injury. The first part of the book, "General Considerations Pertaining to Traumatic Disabilities of the Upper Extremity," is largely introductory in character and concerns principles applicable almost as much to the lower as to the upper extremities, although mobility is stressed throughout as the predominant requirement for the arm in contrast to stability for the leg. This introductory section emphasizes the close interrelationship of the joints of the extremity and the fact that all joints must be subservient to the proper functioning of the hand. Without this overall picture it is difficult to plan correctly the proper reconstructive procedures.

The second and major part of the book is presented in the form of "case histories" rather than as a text, with special emphasis on clinical and diagnostic features. For this reason it will be exceptionally useful in the handling of individual cases.

Operations for the habitual dislocation of the shoulder joint are discussed at length. The author favors the Nicola and Henderson operations. For unreduced fracture dislocations of the neck of the humerus he advises open reduction or resection. Resection is used in the majority of older injuries al-

though many do not require operation if pain is not an important factor. The massive onlay bone graft is preferred for non-union of the humerus, radius and ulna. The bone is taken from the tibia and fixed with vitallium screws.

Disabilities of the elbow are grouped from the physiologic and functional point of view rather than the anatomical. Cubitus varus and valgus, intra-articular blockage of the elbow, extra-articular contractures, intra-articular adhesions, disabilities following unreduced dislocation, traumatic arthritis, and nerve palsies are presented along with the indicated operations and case reports.

The controversial question of the proper operative treatment of non-union of the scaphoid is answered by giving the following choice of operations with the special indications for each: drilling of the bone, bone graft and resection of the scaphoid.

In the discussion of the deformities of the hand the work of Bunnell is quoted frequently. The use of bone grafts taken from the crest of the ilium and fixed with wires or pins through the medulla is not mentioned. This method, which has been used extensively in Army orthopedic centers for non-union of the metacarpals, has proved to be valuable.

This volume is the work of an authority, excellently written, and supplemented with clear and appropriate illustrations.

W. F., Jr.

Spezielle Chirurgische Therapie. By Dr. Max Saegesser, Privatdozent für Chirurgie, Bern. Pp. 884; 1989 ills. Bern: Hans Huber, 1946. Price, $20.00.

This volume is one of a group of medical handbooks for doctors and students published by Huber. The author has set as his aim the answer to 2 questions: What is the best thing to do in a certain surgical situation and how is this best done? The answers to these questions are definitely and clearly stated in the text. The entire range of surgery from traumatic neurosurgery to fractures and other diseases of the extremities is covered in detail with frequent illustrations to permit the reader to follow easily the anatomy and the steps of the operative procedure prescribed. The detail that is given is much greater than would be commonly found in American textbooks. Every step of the diagnosis and of the operative procedure is described and the postoperative care is written to include all the usual postoperative orders for each day. The various possible postoperative complications are described for each disease separately.

The book lacks a section on anesthesia, and the modern emphasis on nutrition of the surgical patient is not found in the description of the postoperative care. In the section on fractures, the treatments prescribed are similar to those of Boehler.

On the whole, the book is well written. The illustrations are pen and ink drawings that show well what the author wishes to illustrate. L. F.

Pulmonary Edema and Inflammation. By Cecil K. Drinker, M.D., D.Sc., Professor of Physiology, School of Public Health, Harvard University. Pp. 106; 27 figs. Cambridge, Mass.: Harvard Univ. Press, 1945. Price, $2.50.

This Harvard University Monograph in Medicine and Public Health includes a series of 4 lectures by the author in which the processes involved in the formation and removal of pulmonary transudates and exudates are analyzed. A fifth chapter upon artificial respiration has been added.

Few authors write in as clear and entertaining a fashion as does Dr. Drinker. In this monograph he has presented a potentially difficult subject so masterfully that even a physician only mildly interested in the subject will read it as easily as a novel. Much of the experimental work reported in this book has been carried out by Dr. Drinker and his associates and he recounts this work as a series of adventures in pulmonary physiology. It is indeed refreshing to turn to this type of presentation and it is hoped that more authors will present their investigations in such personal form. J. C., Jr.

Technique of Psychoanalytic Therapy. By Sandor Lorand, M.D., Member of the Faculty of the New York Psychoanalytic Institute. Pp. 251. New York: International Univ. Press, 1946. Price, $4.50.

In this volume the author presents material used in an advanced seminar and colloquium in technique at the New York Psychiatric Institute. The book presumes in

the reader some knowledge of basic psychoanalytical theory and is meant primarily for the psychoanalyst in training. The author stresses flexibility in technique and interpretation and refreshingly states that at times the therapist must be satisfied with practical results which enable the patient to get along better than he did prior to therapy.

The author uses partial case histories to illustrate problems in technique. Partial contents: Anxieties and Phobias; Sexual Difficulties; Compulsion Neuroses; Dream Analysis; Counter Transference, Termination. J. W.

X-RAYS AND RADIUM IN THE TREATMENT OF DISEASES OF THE SKIN. Edited by GEORGE M. MACKEE, M.D., Professor of Clinical Dermatology and Director, Dept. of Dermatology, New York Post-Graduate Med. School and Hospital, Columbia Univ., and ANTHONY C. CIPOLLARO, M.D., Assistant Professor of Dermatology and Assistant Director, Dept. of Dermatology, New York Post-Graduate Medical School and Hospital, Columbia Univ. Contributor: HAMILTON MONTGOMERY, M.D., Associate Professor of Dermatology, Mayo Foundation, Univ. of Minnesota. 4th ed. Pp. 668; 325 ills. Phila.: Lea & Febiger, 1946. Price, $10.00.

THIS book has fulfilled over the years a demand of radiologists and dermatologists. The historical, engineering and physical considerations of roentgenology and radium are beautifully done by Dr. Edith Quimby. Every radiologist should be thoroughly familiar with the fundamental considerations of radiation therapy, which are beautifully described and illustrated in the text. The biologic and biochemical considerations of irradiation, also considered by Dr. Quimby, are also well done. Dr. Montgomery's chapter on the pathologic histology of radio-dermatitis is excellently prepared and gives important information.

The Reviewer obtains the impression that the factors recommended in the treatment of various lesions under "therapeutic considerations" need to be amplified in order that the inexperienced dermatologist may use this book as a guide. Factors that are used in treatment should be described carefully. The necessity for having frequent measurements made of his machine is stressed in order that he can be sure of its output. This has been done to a considerable extent in some lesions such as tinea capitis. Other chapters such as the one on angiomas of the skin and epitheliomas need much more elaboration.

The authors have had a tremendous amount of experience and they have done a great deal to elevate the standards of radiation treatment in dermatologic conditions. It is hoped, therefore, that in any subsequent editions more detailed consideration of treatment techniques will be included.

Many of the references in the Bibliography refer to older publications on the various subjects. Though these are important, the Reviewer believes that it is equally important to deal with some of the more recent pathologic considerations of the conditions and the radiologic methods employed in their control.

This is one of the best books on the subject. It contains a wealth of information, is concisely written, and well illustrated. The publishers are to be congratulated on the physical quality of the book including the paper, print and illustrations. E. P.

MEDICAL CLINICS OF NORTH AMERICA. Boston Number. Philadelphia: W. B. Saunders, 1946. Price, $16.00 a year.

THIS issue is described as a Symposium on Specific Methods of Treatment. It contains articles on a wide variety of diseases, and will prove of value to the internist as well as to the general practitioner. Some of the papers discuss the present status of new drugs, such as streptomycin, demerol, benadryl and pyribenzamine. Others cover adequately and in sufficient detail such general problems as virus diseases, essential hypertension, renal insufficiency, coronary occlusion, and chemotherapy in diseases of the ear, nose and throat. The paper on infectious hepatitis summarizes the recent advances resulting from the careful study of large numbers of cases in the Armed Forces and in civilian hospitals. "Postwar Tropical Diseases" mentions the problems which will arise from time to time in civilian practice, but fails to give specific directions for the treatment of an average case of malaria, and mentions only in general terms the treatment of amebiasis, which may well prove to be a far more important problem. If the recommendations for the treatment

of anemia and of neurocirculatory asthenia were more widely followed, such patients would be greatly benefited. H. H.

EARLY AMBULATION AND RELATED PROCEDURES IN SURGICAL MANAGEMENT. By DANIEL J. LEITHAUSER, M.D., F.A.C.S., Chief of Surgery, St. Joseph Mercy Hospital, Detroit. Pp. 232; 36 figs.; 6 tables. Springfield, Ill.: Charles C Thomas, 1946. Price, $4.50.

DURING the recent war the Reviewer had an opportunity to see the effects of an extreme form of early ambulation in many hundreds of Chinese patients who refused to limit their activities after operation. A walk of a mile or so on the day after an abdominal operation was not unheard of. It would be well for a surgeon who has any doubts as to the benefit of early ambulation to read and reread this book until convinced that this method of treatment is not only harmless but beneficial.

There is so much of value in this presentation that it seems petty to call attention to minor inaccuracies and omissions, but there is one suggestion that might be made. If another edition is contemplated, Dr. Leithauser might well expand the section on preoperative management, placing more emphasis on nutrition, for this is of great importance to the patient in the postoperative period. I. R.

MONGOLISM AND CRETINISM. A Study of the Clinical Manifestations and the General Pathology of Pituitary and Thyroid Deficiency. By CLEMENS E. BENDA, M.D., Director, Wallace Research Laboratory for the Study of Mental Deficiency, Wrentham, Mass., Instructor in Neuropathology, Harvard Medical School. Pp. 310; 103 ills. New York: Grune & Stratton, 1946. Price, $6.50.

THIS book represents data collected during 10 years of research. More than 300 patients with mongolism were studied, 50 of whom came to autopsy. The author gives evidence for his concept of mongolism as pituitary deficiency occurring in fetal life, with growth disturbances following specific patterns, and states that "the mental deficiency is the result of a chronic deficiency of oxygenation or sugar metabolism."

He states that a degenerating goiter in cretinism sometimes causes toxic symptoms of "dysthyroidism" and makes total thyroidectomy preferable to leaving intact the degenerating goiter which causes dysfunction. This is not consistent with modern views that thyroid secretion is never an abnormal secretion qualitatively but varies only quantitatively.

Theoretical discussions, such as those dealing with the functional significance of histologic changes in pituitary and thyroid, are not convincing. However, anyone interested in these 2 conditions will find readily accessible the author's extensive data on gross and microscopic alterations in organs, especially those of internal secretion, the brain, and osseous system, roentgen ray findings, metabolic, hematologic and biochemical studies, behavior and maternal condition. These factual data can be separated from personal points of view and interpretations with which some readers will not be in agreement. I. Z.

THE SURGICAL TECHNIC OF ABDOMINAL OPERATIONS. By JULIUS L. SPIVACK, M.D., LL.D., Associate Professor of Surgery, Univ. of Illinois Coll. of Med. 4th ed. Pp. 712; 682 ills. Springfield, Ill.: Charles C Thomas, 1946. Price, $10.00.

THIS textbook is now in its 4th edition. It is a precisely written and carefully printed book on operative technique. The illustrations are diagrammatic rather than anatomic.

The Reviewer believes that in the next edition the author should feel it his responsibility to eliminate from it futile and even dangerous operative procedures. There is no place in a modern surgical technique book for a description of the use of the Murphy button or for gastroplication. These and a number of other methods belong in a history of surgery.

It might be pointed out also that certain anatomic inaccuracies should be corrected. Figure 235, for example, carries the title "fundusectomy;" but the clamps are shown applied to a section of the body of the stomach below the fundus. Again in Figure 303 the greater curvature is shown lying over the pedicle of the spleen with the fundus well out of the operative field; but the text, referring to the illustration, cautions against injury to the fundus.

In spite of these criticisms the book has the virtue of clarity and conciseness and is undoubtedly useful to interns and residents as a visual aid to understanding the procedures to be followed in the operations described. I. R.

THE DIAGNOSIS AND TREATMENT OF BRONCHIAL ASTHMA. By LESLIE N. GAY, PH.B., M.D., Assistant Professor of Medicine of the Johns Hopkins University, School of Medicine, Director of the Allergy Clinic of the Johns Hopkins Hospital. Foreword by WARFIELD T. LONGCOPE, A.B., M.D., Professor of Medicine of the Johns Hopkins University School of Medicine, Physician-in-Chief of the Johns Hopkins Hospital. Pp. 334; 80 ills.; 4 plates. Baltimore: Williams & Wilkins, 1946. Price, $5.00.

A SOUND presentation of a complex subject and in keeping with the training and rich experience of the author. Chapters deal with the physiology of normal respiration and the asthmatic state, the etiology of asthma, its pathology, its diagnosis, the complications and differential diagnosis of asthma, asthmatic paroxysms, due to psychosomatic disturbances, and the treatment of asthma. Particularly well done are the chapters on pathology and on treatment. There are numerous illustrative case reports that enhance the value of the book. The many therapeutic measures that have been used in this disease are evaluated and the advice offered is conservative and dependable. The discussion of the relation of psychosomatic disturbances to asthma is perhaps more favorable to the psychiatric approach than the evidence warrants, but is fairly put. General practitioners and allergists will find it a helpful addition to their library. R. K.

ACTIONS AND USES OF DRUGS, A TEXTBOOK FOR NURSES. By WINDSOR C. CUTTING, M.D., Professor of Therapeutics, Stanford University. Pp. 326; 27 ills. San Francisco: Stanford Univ. Press, 1946. Price, $3.00.

CONSIDERING the limitations of background of student nurses and the time usually allotted to a nurse's course in Pharmacology, this text seems to be a most sensible approach to the subject. The fact that the book does not adhere closely to the course outline given in *A Curriculum Guide for Schools of Nursing* and the omission of many rather obsolete drugs, often included in this course, are well compensated for by the logical, basic approach to this science and by the inclusion of many of the newer drugs in wide use today. Each illustration is simple, meaningful and enlightening. H. R.

NEW BOOKS

Chemotherapeutic and Other Studies of Typhus. By M. VAN DEN ENDE, C. H. STUART-HARRIS, F. FULTON and J. S. F. NIVEN, *et al.* Medical Research Council, Special Report Series No. 255. Pp. 246; 11 ills. London: His Majesty's Stationery Office, 1946. Price, $3.65.

A Laboratory Manual of Physiological Chemistry. By WILSON D. WRIGHT. 6th ed. Pp. 275. Baltimore: Williams & Wilkins, 1947. Price, $2.50.

The Story of Human Birth. By ALAN FRANK GUTTMACHER, M.D. Pp. 224; 7 ills. New York: Penguin Books, 1947. Price, $0.25.
A REPRINT of Dr. Guttmacher's book entitled "Into This Universe."

Neue Wege in der Diagnostik und Therapie der Lues. By A. ROTTMAN. Pp. 128. Vienna: Verlag Brüder Hollinek, 1946. Price, $9.50.

Chemotherapeutic and Other Studies of Typhus. Special Report Series No. 255. Price, $3.65.

Primeros Cuidados a un Accidentado. Por El DR. L. GUBERN SALISACHS, Exprofessor A. por oposicion de la Facultad de Medicina de Barcelona. *Complicaciones de la obesidad.* Por el DR. RICHARD A. FAUST. *Diagnostico precos del carcinoma uterino.* Por el DR. JOE VINCENT MEIGS. *Indicaciones y forma de aplicación de penicilina en dermatologia.* Por el DR. M. CASANOVAS. Pp. 203; 65 ills. Barcelona: Coleccion Espanola de Monografias Médicas. Vol. 58, 1946. No price given.

Compresiones Medulares. Coleccion Espanola de Monografias Médicas. Vol. 55. Por el DR. IGNACIO DE GISPERT CRUZ. Pp. 135; 39 ills. Barcelona: Ediciones Byp, 1946. Price not given.

Tratamiento Actual de la Sifilis. Coleccion Española de Monografias Médicas. Vols. 56–57. Por el DR. MODESTO CASANOVAS. Pp. 169. Barcelona: Ediciones Byp, 1946. Price not given.

Étude des troubles causés par la dénutrition dans un asile d'aliénés. Par MAURICE BACHET, Externe en premier des Hopitaux de Paris, Interne de la Maison de Charenton. Pp. 269. Paris, Louis Arnette, 1943. No price given.

Three books by D. DANIELOPOLU, Professeur de Clinique Médicale à la Faculté de Médecine de Bucarest:

Le Système Nerveux de la Vie Végétative. I-ere Monographie. *Schema Anatomo-Physiologique du Système Nerveux de la Vie Végétative.* Pp. 443; 159 ills. 1944.

Phylaxie—Paraphylaxie et Maladie-specifique. Pp. 285; 91 ills. (n.d.).

La Digitale et les Strophantines. Pp. 206; 56 ills. 1946.

Paris: Masson et cie. No prices given.

Chemotherapy, Yesterday, Today and Tomorrow. The Linacre Lecture 1946. By SIR ALEXANDER FLEMING. Pp. 39; 2 ills., 5 figs. Cambridge: University Press; New York: Macmillan, 1946. Price, $.50.

Directory of Medical Specialists Holdings Certification by American Boards. Vol. III. Edited by PAUL TITUS, M.D., and associates. Pp. 896. Chicago: A. N. Marquis, 1946. No price given.

BESIDES including all the changes to date of the examination requirements of all Boards, this 3rd edition contains "much entirely new biographic information."

Tumores y Seudotumores de la Mama. Por el DR. JACINTO MORENO. Pp. 139; 40 ills. Buenos Aires: Lopez & Etchegoyen S.R.L., 1947. No price given.

A BRIEF review of the pathology, a discussion of the classification and a rather pessimistic view of the therapeutic possibilities based on personal impressions.

La Enfermedad de Besnier Boeck Schaumann. By ST. J. LEITNER. Coleccion Espanola de Monografias Médicas, Vols. 59–60. Pp. 240; 37 ills. Barcelona: Ediciones Byp, 1946. No price given.

A SPANISH translation of the German language monograph published in Bern, Switzerland, in 1942. It is based on a study of 15 cases and an exhaustive review of the literature, especially European. The clinical and classifactory aspects are particularly well covered. The question of tuberculous or non-tuberculous etiology is unbiasedly considered and left as undecided. This small volume presents a thorough coverage of the subject. The illustrations leave much to be desired technically.

NEW EDITIONS

Handbook of Microscopic Characteristics of Tissues and Organs. By KARL A. STILES, M.S., PH.D., Professor of Biological Science, Michigan State College. With an Introduction by MELVIN H. KNISELY. 3rd ed. Pp. 214; 33 ills. Philadelphia: Blakiston, 1946. Price, $1.75.

THIS handbook attempts to separate the subject matter required for immediate use from that needed for reference. It "is designed to be used supplementary to a regular textbook of histology. . . . It may be used as a syllabus with lectures. It can be used as a laboratory manual. . . . It has proved its worth for purposes of review to students of pathology."

Principles of Animal Biology. By A. FRANKLIN SHULL, Professor of Zoology, University of Michigan, in collaboration with GEORGE R. LARUE and ALEXANDER G. RUTHVEN. 6th ed. Pp. 425; 305 ills. New York: McGraw Hill, 1946. Price, $4.00.

THIS edition of a useful book includes changes that stress the modern preoccupation with function.

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